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THE CONTRIBUTIONS OF ENZYMOLOGY TO NEUROCHEMISTRY[1]

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The appreciation of the role of enzymatic constituents of the nervous system in controlling its metabolic events, and of the connection between brain metabolism and functional behavior of the central nervous system, has developed as a result of investigations carried out during the last few decades. Interest in the dynamic biochemical concepts emanating from these investigations has intensified recently when it has become apparent that some aspects of mental disorder may find an explanation in the abnormal biochemical behavior of the brain.

OXYGEN AND THE BRAIN

It was early realized that the brain is highly vulnerable to oxygen lack, a continuous supply of blood being essential for the normal functioning of this organ. An interruption of cerebral circulation for only six to eight seconds will produce loss of consciousness. The mental effects of cerebral anemia have been frequently described (45). It was also known, however, that unconsciousness may occur without a preliminary cerebral anemia or fall in cerebral blood flow. There seems to be no decrease in total cerebral blood flow during sleep or in epileptic seizures (44). It was evident, therefore, that although the unconscious state may take place as a consequence of lowering the oxygen supply to the brain it may also occur when oxygen is as freely available to the cerebral tissues as in the conscious condition. Lennox (66) pointed out that acute anoxia may produce nervous symptoms not observed in states of chronic oxygen lack. Moreover, he showed (67) that seizures of epileptic patients can be regularly induced by administration of air deficient in oxygen. Conversely an increased oxygen pressure will diminish the number of seizures in an epileptic patient. High oxygen pressures will, however, induce convulsions, a fact known since 1878 (13). A constant, rather than a rich, supply of oxygen is essential for the normal functioning of the brain, a fact that points to the importance in the central nervous system of the regulation, within certain narrow limits, of respiratory activities and of the various metabolic events dependent on respiration. Many of the consequences of oxygen lack, both physiological and psychological, as well as intellectual impairment were well known many years ago (8).

These facts, pointing to the dependence of intellectual and cerebral function on oxygen supply, created considerable interest in the amount of oxygen supplied to the brain and in the significance of neuronal respiratory mechanisms. The flow of blood through a rabbit brain was estimated at 60 ml. per 100 grams per minute, and through a human brain at about 70 ml. per 100 gram per minute (124). Recent, and doubtless more accurate, figures, due to Kety and Schmidt (60) show that 54 ml. blood flow through 100 g. young adult human brain in one

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minute. This indicates that in the resting adult the brain receives one sixth of the blood supply by the heart. The oxygen consumption of the brain is certainly high. Hou calculated, over thirty years ago (55), that 5.6–7.8 ml. oxygen were consumed by 100 g. dog brain per minute. Recent results (60) show that young adult human brain consumes 3.3 ml. oxygen per 100 g. per minute, indicating that the brain consumes one fifth of the total oxygen used by the body. Folch (33) has calculated that during the first four years of life more than one half of the total oxygen consumption of the body is by the brain. The normal blood flow and oxygen saturation of the blood seem to be adequate to supply the brain's respiratory demands. According to Lennox (66) the oxygen content of the blood leaving the human brain is about 60 per cent of the saturation value.

Some of the earliest results on the respiratory activity of the brain *in vitro* are due to Warburg *et al.* (121), who had in 1923 introduced the tissue slice technique for the study of tumour metabolism. Rat grey cerebral cortex in presence of a glucose-Ringer medium yielded a Q_{O_2} of 10.7, while retina gave the remarkably high figure of 30.7. Although higher figures for the Q_{O_2} of cerebral cortex slices have been recorded, *e.g.* 14.5 by Loebel and 19.1 by Jowett and Quastel (71), these values are lower than those calculated from those obtained by the study of brain *in vivo*. Although it is possible to increase the Q_{O_2} values of cerebral cortex slices by addition of various substrates to a glucose-Ringer medium (65), the disparity between the *in vivo* and *in vitro* values may be due partly, if not wholly, to an activation mechanism operating under *in vivo* conditions. It is known that changes of cation concentration in the medium bathing the brain tissue *in vitro* may result in a doubling of the respiratory rate. Electrical stimulation has a similar enhancing effect. Such activation phenomena, whose importance biochemically is now becoming recognized, separate enzymatic studies carried out with "resting" or unstimulated brain tissue or other nerve preparations from those of nerve tissues stimulated by cationic changes or by application of electrical impulses.

Very early studies showed the presence of cytochrome oxidase activity in brain, *e.g.* those of Vernon (117, 118) who showed that indophenol oxidase activity of the brain varied inversely with the size of the animal, a fact confirmed by Quastel and Wheatley (100). The suggestion was made (94) that the inverse relationship is due to varying proportions of gray to white matter in the brains of these animals, the smaller animal having the greater proportion of gray matter. The strong inhibitive action of cyanide on normal respiration of the brain pointed to cytochrome oxidase being quantitatively the most important mechanism in the brain for oxygen activation. There is a considerable increase in the activity of brain cytochrome oxidase during post-natal growth (50). Potter *et al.* (90) have observed that this enzyme is low in activity at birth (in the rat) and increases steadily during the first month of life. It is presumably absent in the early stage of fetal development. These facts are to be correlated with observations in the rat (115) and in the dog (49) which have led to the conclusion that newer parts of the brain respire at a slower rate than the older portions at the time of birth. As growth continues these relative positions are reversed and the metabolic rates of the newer parts of the brain take the lead. In contrast with the newborn animal the adult rat exhibits the highest rate of metabolism in the phyletically newest parts of the brain (46). The increasing rate of metabolism of the brain as whole, with age, is to be attributed largely to the increasing rate in the newer parts of the brain during early life (46).

GLUCOSE METABOLISM IN THE BRAIN

The respiratory quotient of the brain *in vivo* was known many years ago to be about unity, pointing to the probability that

carbohydrate is the main fuel of the brain. This conclusion was supported by the fact that oxygen consumption is approximately equivalent to the glucose disappearance in the passage of blood through the brain, assuming complete oxidation of glucose (48). Actually, however, under normal conditions about 85 per cent of the glucose obtained by the brain from the blood is oxidized to carbon dioxide, about 13 per cent is converted to lactate and two per cent to pyruvate (41). The average value for normal glucose utilization by the human brain is about 5 mg. per 100 g. brain per minute (59).

In hypoglycemic coma in man, the brain continues to use oxygen at about half the normal rate when the blood glucose has dropped considerably and the amount utilized is negligible (61). It is therefore clear that in the absence of exogenous glucose, the brain may continue to respire and to survive for a short time, but there is no doubt that glucose is the normal and dominant source of fuel for the brain. Glucose, as is well known, restores brain function in insulin hypoglycemia. Fructose is partly utilized by the perfused cat brain, but, as with galactose, hexosediphosphate, or lactose, is ineffective in restoring brain function. Mannose and maltose, however, are almost equivalent to glucose in the restoration of function (76).

It was known many years ago that glucose, fructose and mannose increase the oxygen uptake of excised minced brain tissues (71, 27, 101). Quastel and Wheatley (101) studied the oxidations of brain tissue that had been allowed to deplete itself largely of oxidizable material, prior to the addition of a substrate, by autoxidation for two or three hours. They showed that, of all sugars tested, glucose, fructose and mannose had the largest effects in restoring the rate of respiration to nearly the initial value. Galactose had a small effect but mannitol and the pentoses were inert. They also showed that the addition of lactate and pyruvate to minced brain tissue, partly depleted of metabolites by autoxidation, restored the rate of respiration to almost the initial level. This delayed substrate technique was used later by Peters and his colleagues with the brain tissue of pigeons suffering from avitaminosis B_1 and they demonstrated that such tissue respires at a smaller rate than normally in presence of glucose or lactate, and that the addition of vitamin B_1 *in vitro* restores the ability of the brain to respire at a normal rate. The effect of the vitamin was found to be intimately associated with the oxidation of pyruvate (36). Thus, it became apparent that the well known nervous disorder, consequent upon vitamin B_1 deprivation, was due primarily to a defect in carbohydrate metabolism in the brain, the defect being associated with pyruvic acid oxidation.

The ability of brain to consume carbohydrate was also shown by its high rate of anaerobic glycolysis (121). In fact the view was held at one time (54) that glucose oxidation in brain proceeds through the intermediate production of lactic acid. This conclusion was shown to be untenable by the finding that a competitive analogue of lactic acid, *viz.* tartronic acid, inhibits respiration of brain in presence of lactate to a greater extent than that in presence of glucose (56). Nicotine, by a mode of behavior as yet unexplained, also has the same effect (7).

The sensitivity of brain to oxygen and glucose was shown many years ago by the fact that the deprivation of brain tissue of both oxygen and glucose for short periods (*e.g.* five minutes) very greatly decreased the rate of anaerobic glycolysis when glucose is subsequently added to the tissue (25) and, in fact, it was concluded that anaerobiosis, in absence of glucose, brings about irreparable damage to the brain. It was shown, however, (104) that, if brain tissue which has been kept anaerobically in the absence of glucose is subsequently exposed to oxygen, its power of bringing about anaerobic glycolysis may be almost completely restored.

Although brain has a markedly high ana-

erobic glycolytic rate, its rate of aerobic glycolysis . (121) is small. Presumably energy for the brain's metabolic activities comes largely from oxidative breakdown of glucose. How far anaerobic energy, derived by glycolysis, may be important for some aspects of the activity of the nervous system is still unknown, but there is no reason as yet to regard it as quantitatively significant except in the brain of the newborn. There is, however, the possibility that glycolysis is concerned in the regulation of pH with consequent effects on brain circulation (28). In this connection, too, it is well to point out that an enzyme that plays an important role in pH regulation, namely carbonic anhydrase, is present in the brain, in amounts which fluctuate in mental disorder (2).

The fact that oxidative metabolism of glucose plays a dominant role in the dynamic biochemistry of the brain has made the study of the enzymes concerned important for an understanding of the relations between brain metabolism and brain function. For this reason, the enzymes involved in the familiar Embden-Meyerhof scheme for glucose breakdown to pyruvic acid and those involved in the oxidation of pyruvic acid by the citric acid cycle of operations have received, and will continue to receive, much attention (*e.g.* Coxon, 22). The alternate glucose oxidation pathway, known nowadays as the pentose phosphate shunt (24), is beginning to attract attention as a possible brain mechanism. It is well to realize that vitamin B_1 (as thiamine pyrophosphate), is a cofactor for transketolase (105) which is involved in the pentose phosphate cycle. If so, deprivation of the brain of thiamine may effect the "pentose phosphate shunt" as well as the metabolism of pyruvic acid itself.

Two enzymes, in particular, have assumed major importance in the degradation of glucose, *viz.* hexokinase which is probably responsible for initiating the metabolic reactions of glucose, and triosephosphate dehydrogenase which controls the rate of energy production from glucose-6-phosphate. Interferences with these enzyme systems will undoubtedly affect brain metabolism and function, but no one can doubt that all the enzymes involved in the sequence of events leading to the complete oxidation of glucose in the brain must play a role in the overall activity of the brain. Time alone will show their relative quantitative importance. Mention must be made, in this brief appraisement of the significance of carbohydrate breakdown in the brain, of the vital importance of the various coenzymes, and of the enzymes that govern their syntheses, breakdown and interconversions. There can be no doubt that the ratios ATP/ADP, DPN/DPNH, FAD/FAD·H_2 are as significant for the direction of chemical events in the nervous system as the presence of the cytochrome components, cofactors such as thiamine, coenzyme A, and glutathione and the various enzymes that activate the substrates involved. In the growth of dynamic concepts in neurochemistry, the enzymes governing the sequential steps involved in sugar breakdown are of major importance.

It has been pointed out by Geiger (37), as a result of his recent perfusion experiments, that the liver contributes substances, possibly uridine and cytidine, that are important for normal carbohydrate metabolism in the brain and the maintenance of brain function. Possibly these are concerned with the maintenance of lipid structures in the nerve cells. It is easy to show that venom lecithinase greatly affects brain glucose metabolism by an attack on both mitochondrial and neuronal membranes (15, 17) and that therefore the integrity of phospholipid structures is necessary for normal neuronal metabolism.

SUBSTRATES OF BRAIN METABOLISM AND BRAIN FUNCTION

Brain can bring about a variety of oxidative changes, not normally associated with

carbohydrates, besides those involved in complete sugar breakdown to carbon dioxide. It was early known (101) that brain will oxidize L-glutamic acid which was thought then to be the only amino acid capable of oxidation in the nervous system. It is clear now that other amino acids, *e.g.*, glycine (69), undergo oxidative changes in the brain though these are not so important quantitatively. Butyrate and crotonate are not oxidized at appreciable velocities (103) and the brain has little capacity to abstract and utilize ketone bodies from the blood (83). Octanoate, however, undergoes oxidation (110). Lactate and pyruvate which undergo metabolism in the brain are unable to restore, or preserve, function in a manner similar to glucose. Cortical electrical patterns in the hepatectomized animal (76) cannot be restored by administration of glycerol, lactate, pyruvate, succinate, fumarate, acetate, or L-glutamate. Using the perfused thoracic spinal chord of the rat it has been found (113) that the following substances are apparently oxidized but without return of reflex action: acetate, lactate, βhydroxybutyrate, fumarate, malate, succinate, alanine, lysine, tyrosine, aspartic acid and cysteine. The following however, restore full reflex action: pyruvate, αketoglutarate, glutamate and glutamine. Both glutamate, and apparently, glycine, can restore conscious behavior in patients in deep insulin coma, though succinate is ineffective (82). Weil-Malherbe (123) has shown arousal from insulin coma among patients receiving glutamic acid glycine or succinic acid. It is possible that the effects of some of these compounds are indirect, by conversion in the body to glucose. There is no doubt that the blood-brain barrier plays a remarkable part in its insulation of the brain to a large variety of substrates which are present in the blood (112) and which might be thought, from the results of experiments *in vitro*, greatly to influence brain metabolism and function.

BLOOD BRAIN BARRIER

The concept of the blood brain barrier arose from experiments by Ehrlich in 1885 when he showed that certain dyestuffs which stain most tissue are not taken up by the central nervous system. The acid dye, Trypan blue, was shown by Goldmann to be the type of dye that only stains after intrathecal injection or following excessively high intravenous dyes. In this connection it is of interest to note that dyes which have large inhibitory effects on the oxidations of muscle tissue have little or none, under the same experimental conditions, on brain tissue (99). In fact it was concluded that the enzymes in the excised brain tissue are protected either by an inability of the dyes to reach the site of the enzymes in the cells or because constituents are present that combined preferentially with them. The intracellular enzyme, fumarase, which is richly distributed in brain, is poisoned by minute concentration of acid dyestuffs such as Trypan blue (93). It is evident that, both *in vivo* and *in vitro*, a barrier is presented by nerve cell membrane to substances that appear to have much easier access to the cell interior in most other tissues. However, there is little doubt that substances, which undergo rapid metabolism by the brain *in vitro*, in the form of minced tissue or slices, *e.g.* succinate or lactate, show little evidence of equally rapid breakdown in the brain *in vivo* when administered intravenously. This is not the place to discuss the implications of the blood brain barrier, but to point out that it must be considered in our concepts of the dynamic biochemistry of the central nervous system. The net effect of the existence of this barrier is to give the brain a unique insularity from a variety of biochemical changes in the blood, which doubtless secures a greater uniformity of chemical events in the nervous system. Disturbances in this barrier, possibly brought about by cation changes or changes of pH, may well have far reaching effects on the bio-

chemistry of the brain as a whole. There seem to be changes in the barrier according to age, for according to Himwich (51) glutamic acid enters the brain of one day old rat, though it apparently cannot increase the brain concentration of glutamic acid in older animals. It is obvious that in the modern search for substances that affect the metabolism of the brain and its function, the properties of the blood brain barrier, both in the young and the adult animal, must receive consideration.

SYNTHESES INVOLVING CHOLINE

Important in the growth of concepts of the relation between brain biochemistry and brain function has been the discovery of the role of brain mechanisms in the synthesis of acetylcholine. This substance, known to play a major role in the physiology of the brain (21), undergoes rapid hydrolysis by choline esterase, whose activity in various parts of the brain is of obvious importance to brain function. The pharmacological effects of choline esterase inhibitors, of which there are a great variety, point to the significance of this enzyme in neurophysiological and neurochemical phenomena. This is seen not only in the effects of quaternary ammonium bases, of prostigmine and its analogues, of curare etc. in man and higher animals but in the effects of anticholinesterases such as fluorphosphonates and polyphosphates and substances that have obtained economic importance as insecticides. The existence of a choline esterase inhibitor, eserine, made it possible to demonstrate for the first time in 1936 the synthesis of acetylcholine by brain cortex slices under physiological conditions (98). It was shown that the synthesis by brain slices could only be effected aerobically in presence of glucose, mannose, pyruvate or lactate. Glutamate and alpha glycerophosphate were effective to a small extent, but succinate and fructose and galactose and acetate were ineffective. It was suggested that energy derived from carbohydrate breakdown was responsible for synthesis of acetylcholine, and the results indicated a link between glucose metabolism and a biosynthesis such as that of acetylcholine. Moreover, brain was almost unique in this property for neither kidney, spleen, liver nor testis showed the synthesis, and muscle showed it only feebly. Stedman (111) later demonstrated acetylcholine formation in brain, but his results showed little evidence of biosynthesis but rather the fact that a bound, pharmacologically inert form of acetylcholine could under his experimental conditions liberate free acetylcholine. It is very likely that this bound form of acetylcholine is mitochondrial-held acetylcholine liberated when the mitochondrial structures are destroyed (16). The discovery of acetylcholine synthesis by enzymatic means had considerable consequences, for it was the first demonstration *in vitro* of an enzyme controlled acetylation. Nachmansohn and Machado (85) showed later that this synthesis will occur anaerobically with an acetone powder extract of brain so long as adenosine triphosphate (ATP) is present. It became obvious that the ATP derived from carbohydrate metabolism in the brain can be utilized for a brain acetylation. Further work made it clear that the synthesis was dependent on a heat stable cofactor (84) studied by Nachmansohn, by Feldberg and by Lipmann who with his colleagues showed its importance, as coenzyme A, in acetylation and biosynthetic processes. It is evident that ATP plays a vital role in the dynamics of neurochemistry, not only because of its importance in the mechanics of carbohydrate breakdown and oxidations, but because of its role in many of the synthetic events of the nervous system. The recognition that ATP is itself synthesized by oxidative reactions that occur in the brain has made the study of oxidative phosphorylations a subject of paramount importance in neurochemistry.

It is well, at this point, to mention another

link between ATP and the reactions of choline, namely the synthesis of phospholipids (109) which are well recognized constituents of brain, and whose functions in the dynamics of neurochemistry are only now beginning to be recognized.

Choline, under the influence of ATP, forms phosphocholine, which through the operation of cytidine-triphosphate and an appropriate enzyme forms cytidinediphosphocholine. This, in turn, condenses with a 1:2 diacyl glyceride, produced by the operation of acetyl-coenzyme A on alpha glycerophosphate, to form alphalecithin. Thus the details of phospholipid synthesis in brain are becoming clearer and the operational enzymes involved will loom larger in the concepts that link brain metabolism with brain function.

CATIONIC EFFECTS

The role of cations in neurochemical kinetics is beginning to assume an importance even approaching that held for the cations in neurophysiology. This, of course, is most desirable, and there is little doubt that neurochemistry will take a major step forward when many of the phenomena of neuropharmacology and neurophysiology will receive a satisfactory interpretation on a neurochemical basis.

It was known over 20 years ago (3) that the metabolism of brain cortex slices is greatly influenced by the cation composition of the medium in which the brain tissue is immersed. The addition of 0.1 *M* KCl to a Ringer medium containing glucose brought about increased rates of respiration and aerobic glycolysis and a decreased rate of anaerobic glycolysis. Further studies at the same time (26) indicated the difficulty of assigning a special role to a given cation owing to the interaction taking place in the presence of mixtures of ions. The high rate of aerobic glycolysis by brain when sodium is the only cation present is almost abolished by the presence of potassium, which, however, when added at the high concentrations (0.1 *M*) that occur in the cell interior, increases aerobic glycolysis. But these changes in metabolism, produced by cationic changes, do not occur with kidney cortex, testis, retina and tumor tissues. Thus the cation effects on brain metabolism were thought to be due to changes in brain cell permeability. The effects of cationic change, so marked on aerobic metabolism of brain *in vitro*, are equally well marked on its anaerobic metabolism. Calcium ions greatly stimulate anaerobic glycolysis in contrast to the effects of potassium and moreover a variety of organic bases have effects resembling those of calcium (1, 104). These phenomena, on the whole, are unique for the brain. The results indicate that the neuronal membrane is a rate limiting factor in cellular glucose metabolism (97), and that the cations sodium, potassium and calcium must be considered as important for the consideration of the kinetics of neurochemistry as the cofactors and the enzymes themselves.

NARCOTICS, ANESTHETICS AND TRANQUILIZERS

In the hope of throwing light on the mode of action of narcotics in the body, and on a possible relationship between biochemical changes in the central nervous system with the narcotic state, experiments were carried out over 25 years ago on the effects of narcotics on brain respiratory systems (101). It is now well known as a result of these and many succeeding investigations (95) that narcotics, with the exception of the alkaloid group containing morphine and allied substances, have the power at low concentrations of inhibiting the respiration of isolated brain tissue in presence of glucose or pyruvate, especially if this is examined in the form of intact slices or as brain mitochondria. This conclusion applies to local anesthetics, to chlorpromazine and to the steroid narcotics. There is, in fact, a close correlation among narcotics and anesthetics of different chemical types between hypnotic activity and

respiratory inhibition. The high sensitivity to narcotics and anesthetics of glucose oxidation in the brain is a striking feature of narcotic action *in vitro*. Such observations made it seem possible that the interference with brain function, accomplished by narcotics and allied substances, is related to changed metabolic events in the nerve cell as a result of the presence of the drug. The concentrations of narcotics required to accomplish inhibitory effects on neuronal metabolism were, however, so large compared with those required to induce narcosis that the affected reactions were thought to have no relation to the narcotic state. Further work, nevertheless, made it clear that narcotics, at low pharmacological active concentrations, exhibit two phenomena:

1) the uncoupling of phosphorylation from oxidative processes (19) which is followed by a depressing effect on total oxygen consumption,

2) the suppression of neuronal respiration that has been stimulated either by application of electrical pulses (74) or by exposure to a potassium ion concentration approximately equal to that in the neurone itself (40).

The high sensitivity of stimulated nerve respiration to chloretone, which had been noted by Bronk and Brink in 1951 (20), made the mechanism of potassium stimulation of glucose respiration of brain of importance in connection with brain function. Apparently the effect of the presence of potassium ions is to stimulate a rate limiting step in the citric acid cycle operating in brain respiration, but the precise nature of this step and its site in the nerve cell are at present unknown, though the neuronal, or perhaps the mitochondrial, membrane is implicated (96, 11). It is worthy of mention that with the unstimulated or "resting" brain cortex slice glucose is not fully oxidized but is transformed partly into amino acids (12, 37), and other substances. This is shown by the use of uniformly labelled glucose. When stimulation of respiration occurs by the addition of potassium ions the increased glucose utilized is accounted for by almost complete oxidation to carbon dioxide and water (97a).

It is of interest that the stimulation of brain slice respiration due to electrical impulses takes place with the same substrates (glucose, pyruvate, lactate) which permit responses to the action of potassium ions. All the evidence points in fact to the similarity in many respects of the biochemical effects of electrical stimulation of the brain slice with those of potassium salts at 0.1 *M* concentration. Brain homogenates or minces are, as is well known, irresponsive to either forms of activation. The present evidence would indicate that narcotics, anesthetics, a tranquilizer such as chlorpromazine (69), aliphatic alcohols or aliphatic aldehydes (11) exercise a large suppressing effect on the respiration of the activated or stimulated nerve cell, this stimulated respiration being effected by the operation of the citric acid cycle. Presumably in the conscious animal stimulation operates by the action of sensory impulses, and high sensitivity to narcotics etc. of the metabolic activity of the stimulated neurone ensues. This concept of an active metabolism is by no means new (18). It is a concept which will receive more attention and investigation in the future. In the meantime, it is to be noted that a narcotic, such as Amytal, is a highly effective inhibitor of DPNH oxidation and its associated phosphorylations (29), a result that is in accordance with earlier conclusions on the site of action of narcotics in the nerve cell (82a, 95). The known interference of narcotics with the oxidative synthesis of ATP in the nerve cell is reflected by their inhibitory effects on acetylcholine synthesis. Presumably they should interfere with a variety of metabolic processes dependent on oxidative formation of ATP. Rossiter and his colleagues (32) have shown that low concentration of narcotics (chloretone, nembutal) exercise large inhibitions of

P^{32} incorporation (from phosphate) in phosphoproteins and organic phosphorus compounds, in respiring cat brain slices, in presence of glucose.

It is important to emphasize that the effects of narcotics on the metabolism of the nerve cell do not necessarily imply that all nerve cells in the brain are equally affected during narcosis nor that a depression of total brain or body respiration should ensue. As a corollary, it does not follow, from only the fact that there is a fall in brain respiration *in vivo* during narcotic states, that respiratory depression in the nerve cell is a cause of narcosis.

It is pertinent to add that the stimulatory effect of potassium ions on aerobic nerve metabolism is greatly decreased in infant brain (50). The response to potassium increases from the time of birth to 40 days of age. The inhibitory effect of malonate, on brain respiration, which is exercised in the citric acid cycle, also increases with age during the first ten days of post-natal life (114). In accordance with the conclusions that have been mentioned, narcotics such as pentobarbital and alcohol exercise a larger percentage depression of respiration in the adult than in the young rat brain (52).

AMINE METABOLISM

When it was realized that narcotics at low concentrations may exercise depressing effects on nerve cell metabolism and it seemed possible that the behavior of an animal undergoing narcosis may be related to the depression of neuronal respiratory metabolism, an investigation was made to discover whether any substances, which might naturally occur in the body, have, at abnormal concentrations, effects similar to the narcotics. It was thought that, if this was the case, such substances, when present in the nervous system in more than ordinary quantities, might be held partially responsible for abnormal mental manifestations (102). Experiments were made on these lines about 25 years ago, and it was found that amines derived from tyrosine, tryptophane and leucine had effects on brain respiration similar to those of the narcotics. Tyramine, tryptamine, isoamylamine proved to have highly inhibitory effects whereas amines such as cadaverine, putrescine, neurine and ethylamine were without action (91, 92, 102). (Almost a quarter of a century had to elapse before hydroxytryptamine was found to be normally present in the nervous system!). Mescaline and bulbocapnine, both of which give rise to abnormal mental behavior, also gave rise to inhibitions of brain respiratory metabolism. Investigations resulted in the finding in the brain of an enzyme capable of oxidizing amines, including aliphatic amines, tyramine and tryptamine, and this was termed amine oxidase (91, 92). This proved to be identical with adrenaline oxidase (14). Amine oxidase was inhibited competitively by amine analogues of which a good example was amphetamine (78, 79). It was pointed out that the relative stimulatory effects of amphetamine and its derivatives on the central nervous system bore a parallelism to their effects on amine oxidase, a suggestion supported by the later work of Oota (87). The amines on oxidation in the brain give rise to the corresponding aldehydes which have high toxicity to brain respiration mechanisms (11, 78, 79), this toxicity being much higher than that due to the parent amines. The aldehyde undergoes in brain a dismutation to the corresponding alcohol and acid (91, 92), so that it is evident that an aldehyde mutase plays a role in the dynamics of brain chemistry. No attempt has been made yet to explore its possible role in brain function. The relatively recent discoveries of noradrenaline and hydroxytryptamine (serotonin) have focussed interest anew on the physiological significance of amine oxidase in brain, for it has been shown by Brodie *et al.* (108) that the amine oxidase inhibitors, ephedrine and iproniazid, suppress the metabolism of the amines men-

tioned and iproniazid administration to rabbits increases their levels in the brain stem. The effects of indole derivatives on brain metabolism are not only demonstrated by the early experiments with tryptamine, indole and skatole (91, 92, 102), but by the new studies with the tranquilizer reserpine and the psychotomimetic drug lysergic acid diethylamide (LSD) which, like serotonin, contain the indole nucleus. Wooley and Shaw (126, 127, 128) have indeed suggested that LSD produces behavioral abnormalities by interfering with the physiological actions of serotonin in the brain. Reserpine apparently frees both noradrenaline and serotonin from their depots. After administration of reserpine to rabbits, brain levels of these amines decline as they are released and destroyed by amine oxidase (108). At present, there is a very active interest being taken in the enzymes concerned with the formation and destruction of products derived from adrenaline and tryptamine because of their psychopharmacological effects (47). Weil-Malherbe has suggested in fact that a connection exists between the level of mental activity and the concentration of adrenaline in the plasma (122).

In connection with the pharmacologically active amines present in the brain, reference must be made to the role of amino acid decarboxylases. Doubtless the decarboxylase that produces serotonin from 5-hydroxy tryptophane which, unlike serotonin, passes from blood to brain (116), or glutamic acid decarboxylase that forms gamma aminobutyric acid will assume increasing importance in neurophysiology and neurochemistry.

AMINO ACID UPTAKE

Glutamate, aspartate, gamma aminobutyrate and glutamine form about 70 per cent of the brain amino acid nitrogen. These substances are normally formed by transaminases in the brain, acting upon alpha ketoglutaric acid and oxalacetic acid formed during carbohydrate breakdown. Subsequent enzymatic operations on glutamate produce glutamine (in presence of ATP) (64) or gamma aminobutyric acid. The role of glutamine in the brain is not yet clear. Unlike glutamate, it passes easily into the brain from the blood. It may be important in peptide synthesis (119, 120), or as a means of transporting ammonia.

Amino acids are taken up by the brain *in vitro* as is easily shown by the use of radioactive compounds. However, the free entry of amino acids into brain *in vivo* is hindered by the blood brain barrier (58). Methionine enters the brain *in vivo* and is rapidly incorporated into the brain proteins, the rate being greater with younger animals. Doubtless protein synthesis and the enzymes involved in amino acid activation and incorporation and the inevitable role of ATP as the energy donor for these operations play their role in brain function. Reactions of amino acids with adenosine or its derivatives, as in the well known example of adenosyl-methionine (Cantoni) may well play a role in amino acid activation and possibly transport. Chlorpromazine, at low concentrations that do not affect the total oxygen consumption of brain, inhibits glycine incorporation into brain proteins (69), presumably by interfering with the aerobic synthesis of ATP needed for this operation.

TRANSPORT PHENOMENA

Much interest is being taken in the components, that resemble enzymes, in cell membranes that control transport into the cell interior. It is well known (23) that brain slices can transport glutamate and potassium ions against a concentration gradient if the necessary energy is provided by glucose breakdown. There is increasing evidence that specific agencies control active transport of sugars and amino acids into the cell interior but relatively little work has been carried out with the brain so far.

Competition of a structural analogue with a metabolite for active transport may prove to have considerable importance in brain function. A recent example is the competition of the hemicholiniums, a series of quarternary bases containing choline moieties, with choline for transport into the neurone (75) resulting in respiratory paralysis. They have the effect of diminishing acetylcholine synthesis in brain tissue but not with a soluble choline acetylase preparation. It is possible that the effects of acetylcholine (in presence of eserine) or of carbamylcholine in causing an increase of labelling of lipid phosphorus in respiring guinea pig and pigeon brain (from radioactive phosphate) (35) is concerned with a membrane transport phenomenon.

CONCLUSION

It is evident as we survey the field of neurochemistry today that the enzymological approach is exercising considerable influence on the minds of those who seek a relation between mental activity and brain chemistry. It has always been my belief that such a relation must exist, and this belief has dominated my own investigations in the neurochemical field since I first became acquainted with mental disorder problems nearly thirty years ago. The subject of neurochemistry in relation to mental behavior has grown rapidly since then in spite, perhaps, of a variety of psychiatric dogmas. It is now developing vigorously and fruitfully, so much so that I feel justified in claiming that in the enzymological approach to neurochemistry we have one of our finest tools for the exploration of the processes of the mind.

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RIGHT-LEFT BODY REACTIVITY PATTERNS IN DISORGANIZED STATES[1]

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INTRODUCTION AND PURPOSE

In preceding studies it has been shown that the relative reactivities of various sectors of the individual's body are linked with the body image attitudes he maintains toward these sectors. Thus, it was found that the ratio of the reactivity of the body exterior to that of the body interior is correlated with the degree of definiteness attributed to the body image boundaries (7). Similarly, it was observed that the differential reactivity of the right vs. left sides of the body is associated with the manner in which the individual has learned to distinguish his right and left sides in his body schema (3, 4, 5). It was also established that individuals who are stable and well organized, especially in terms of body image, manifest different right-left reactivity patterns than individuals who are poorly organized (5, 6). Data were obtained which indicated that right-handed[4] persons with good body image integration manifest a GSR response gradient in which the left body side is more reactive than the right side. However, persons characterized by poor body image integration either show relatively greater GSR reactivity on the right side than on the left or fail to show any consistent differences between the two sides.

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[4] All statements in this paper concerning right vs. left differentiation are restricted to right-handed subjects. It has not been possible to make predictions concerning right vs. left reactivity in left-handed subjects. This special problem with left-handed individuals has been discussed in detail elsewhere (3).

In a related vein, it was discovered that up to adolescence most individuals have not yet worked out a clear-cut body image differentiation between the two body sides and at the same time they rarely exhibit the left GSR reactive pattern which typifies the adult who has a well defined body image (8). The pre-adolescent is either right reactive or without a consistent gradient. But at adolescence many individuals seem suddenly to arrive at a more clear-cut body image differentiation between the right and left sides; and simultaneously about 40 per cent begin to manifest left GSR directionality. It appeared, then, as if developmentally the left reactive GSR pattern was a more mature one than the right reactive or nondirectional patterns.

These findings suggested that factors which make for disorganization or regression in the body schema result in abolishing or diminishing the body reactivity patterns which seem to accompany the mature, well integrated body image. More specifically, it was conjectured that under such disorganizing or regressive conditions there would be a significant decrease of left GSR directionality and an increase in the other reactivity patterns.

Two classes of disorganizing conditions seemed appropriate for exploring the hypothesis. It was considered, first, that an ideal testing situation would be provided by the disorganization associated with schizophrenia. There have been many studies (*e.g.* 1, 2, 10) which have demonstrated that schizophrenic regression is accompanied by unusual and bizarre distortions in the body image. These distortions take such diverse forms as depersonalization, confusion about sexual characteristics of the body, and attributing unusual significances to various

body areas. If the hypothesis which has been proposed is correct, it would be anticipated that schizophrenic patients would be significantly less often left GSR reactive and more often right reactive than normal subjects.

A second means for exploring the hypothesis presented itself in terms of the effects of LSD. There are numerous reports, among which that by Savage (9) is most dramatic, which indicate that a prominent effect of LSD upon normal individuals is to produce changes in their body images. Some of the changes which have been described involve fading of body boundaries, confusion about body symmetry, and radical shifts in apparent size of body sectors. Alterations of this magnitude certainly imply that LSD has a disruptive effect upon the existing body image structure. If such be the case, it would be predicted that normal subjects would manifest left GSR directionality significantly less often and right reactivity more often while under the influence of LSD than during a control period.

SCHIZOPHRENIA CONDITION SUBJECTS

The subjects consisted of 41 male, right-handed patients in the Houston VA hospital diagnosed as schizophrenic. Their median age was 35 years and their median length of total hospitalization for psychiatric treatment was two years. None had received any form of shock treatment for at least six months prior to the experiment. About 60 per cent of the patients had been taking small doses of Thorazine (50 mgms. four times per day). In order to control any differential effect of Thorazine on GSR, most of these patients were removed from the drug 60 hours prior to testing. There were a few who were removed from the drug only 48 hours before testing.

METHODS

The technique for evaluating right vs. left GSR reactivity has been described in detail elsewhere (3). Briefly, it may be said that it is of the exosomatic type. It is based on applying a constant current of 20 microamperes and picking up resistance changes across the skin as changing potentials and feeding them into a Grass EEG amplifier. Recordings from the right and left sides were made simultaneously on separate channels against a relatively inactive upper arm. The recordings were taken at the same time from the two middle fingers; secondly, from the forefingers; then from the ring fingers; and finally from two corresponding points on the palms. There was careful matching of the currents to each finger. The area of recording from the sites was made equivalent by covering each with a piece of tape that had the same sized hole punched into it. The electrodes made contact with the skin only through the punched holes. At least two minutes of recording were obtained from each set of sites. There were finally available for each subject the side by side GSR responses from the homologous sites. Thus, one could compare amplitudes of responses at homologous points at a given time.

The criterion of right vs. left directionality of response was based upon comparisons of the homologous amplitudes. All corresponding responses were noted in which there was a difference in amplitude equivalent to at least 80 ohms. If the differences occurring for a specific site were such that there were twice as many favoring one side as the other and if at least eight such differences were present, then it was judged that a directionality for that site had been demonstrated. Further when it was found that the directionality was in favor of one side for three out of the four sites, it was considered that there was a significant GSR gradient in that direction. When all four sites showed a majority of the differences in the same direction, a less stringent criterion of significant directionality was applied in evaluating any single site. It was then necessary for only five of the differences at any one site to be in the given direction in order to designate that site as showing definite directionality.

TABLE 1

Chi-square Analyses of Differences in Incidence of Right-Left Reactivity Patterns in Normal and Schizophrenic Groups

Groups	Left Reactive			Right Reactive		
	Group with Highest Incidence	X^2	Significance	Group with Highest Incidence	X^2	Significance
Schizophrenics *VS*						
Normal Sample 1	N	4.1	.05–.01	S	2.0	.20–.10
Normal Sample 2	N	6.3	.02–.01	S	4.5	.05–.01

Any given GSR record was categorized as being either left directional, right directional, or without consistent directionality.

RESULTS

The GSR patterns of the schizophrenics were compared with those obtained from two samples of normal males who had been evaluated in previous studies (3, 5). Sample 1 consisted of 35 subjects and sample 2 of 36 subjects. The two samples were comprised in the main of college students; and the median age in both instances was 21 years. The fact that the normal group was younger than the schizophrenic group was not considered to be important because it has been found that there is no correlation between the frequency of the various reactivity patterns and age beyond adolescence.

It can be seen in Table 1 that a chi-square comparison of the frequency of left GSR directionality in the schizophrenic group and in normal sample 1 indicated that it was significantly less frequent (.05–.01 level) in the schizophrenic group.[5] The same comparison of the schizophrenic group and normal sample 2 indicated that left GSR reactivity was significantly (.02–.01 level) less frequent in the schizophrenic group.

[5] It should be noted that there were only chance differences in GSR patterns between those patients who had and had not been taking Thorazine.

A chi-square analysis was also made of the relative frequency of right GSR reactivity in the schizophrenic group as contrasted to normal samples 1 and 2. It was found that right directionality tended to be more frequent among the schizophrenics than in normal sample 1 (.20–.10 level) or in normal sample 2 (.05–.01 level).

Clearly, the overall results support the hypothesis that was being tested. Schizophrenic patients do show less of the left directional and more of the right directional GSR reactivity patterns than do normal subjects.

LSD CONDITION SUBJECTS

Ten normal subjects were paid a fee to participate in the experiment. Six were medical students and the other four were college students. There were eight men and two women.

METHODS

Eight of the subjects took LSD doses of 100 gamma; one of 40 gamma; and one of 20 gamma. Each subject was tested during a control period either the day prior to or the day following the LSD condition. Each subject was also tested during the LSD period within one to two hours after the drug had been administered.

The technique for evaluating right-left GSR reactivity was approximately the same as that described for the schizophrenic group. However, there was one important difference. GSR reactivity was measured from three sets of homologous sites instead of four. The palm sites were omitted.

TABLE 2

Mean GSR Right-Left Reactivity Patterns for Control and LSD Conditions and Significance of Differences between Conditions

GSR Patterns	Control	LSD	Significance of Difference
Left Reactive	1.6	.2	.01–.001
Right Reactive	1.0	2.1	.05–.01
Non-directional	.4	.7	—

RESULTS

Analysis of the data revealed clear differences in GSR right-left patterns from the control condition to the LSD condition. There was tabulated for each subject the total number of control period and LSD period sites which were right or left or non-directional in reactivity. As can be seen in Table 2, there was a significant *decrease* (.01–.001 level) in left reactive patterns from the control period to the LSD condition. One also notes that there was a significant *increase* (.05–.01 level) in right reactive patterns from the control period to the LSD period. The incidence of non-directional patterns was essentially the same for the two sets of conditions. The significant shifts in left reactivity and right reactivity which occurred are obviously congruent with the original hypothesis.

DISCUSSION

The results pertaining to the schizophrenia condition and the LSD condition are mutually supportive and at the same time in the predicted direction. It does appear that disorganized states which are considered to have a disruptive influence upon the body image are accompanied by an increased frequency of immature right-left reactivity patterns. Of course, it is only a presumption that the greater frequency of immature reactivity patterns is due to the disorganization of body image, as such. There are, after all, a variety of functions beside those relating to body image which are adversely affected by schizophrenia and LSD. Indeed, one would be in a stronger position to specify that disturbance of body image is an important variable in the regression of right-left reactivity patterns if body image measures had been taken on the same subjects and if these measures had proven to be correlated with variations in right-left reactivity. However, the techniques which have proven valid in the past for evaluating body image attitudes toward the right and left body sides could not be here utilized because they involve a level of cooperation which would have been difficult for many schizophrenic patients to muster. Also, these techniques have been found to be subject to the influence of practice effects. Therefore, they would have been almost impossible to interpret under the retest conditions associated with the LSD experiment.

However, one may emphasize at this point that it was a theory built upon body image constructs which enabled the successful prediction of disorganization of right-left reactivity patterns in schizophrenic and LSD states. A more specific demonstration of the relationship between disorganized body image and right-left response directionality must await the development of body image measures which are not susceptible to cooperation and repetition effects. Whatever the outcome of future attempts to prove a relationship between body image regression and body gradient disorganization, the fact remains that gradient disorganization is an interesting phenomenon in itself which has not previously been reported. The possibility presents itself that breakdown in the individual is more likely to be reflected in alterations of relationships in levels of reactivity among various body sectors than in gross indices of total body reactivity.

SUMMARY

This study concerned itself with the character of right-left GSR reactivity patterns in disorganized states which presumably disrupt body image integration. It was hypothesized that individuals who were schizophrenic or under the influence of LSD would manifest regressive and immature right-left reactivity patterns to a significantly unusual degree. This hypothesis was clearly supported by the data.

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STERILITY AND THE MAGIC POWER OF THE MATERNAL FIGURE

A Case of Pregnancy After the Decision to Adopt

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The phenomenon of pregnancy occurring in a previously sterile woman after a decision to adopt a child is familiar to medical groups as well as to lay people. The relative frequency with which the wife becomes pregnant just prior to or following the adoption of a baby has, in fact, prompted one writer to point out that stories in this connection are almost a part of our folklore.

That emotional factors figure significantly in the phenomenon of pregnancy in the adoptive mother no less than in the general widespread problem of sterility has been repeatedly stressed by those in the medical profession who are psychologically oriented.

Orr (5) in reporting on pregnancy following adoption, states that, "In many such cases, all the factors except the emotional ones appear to be constant before or after the plan to adopt a child, so that when pregnancy follows it is inferred that the psychologic element must have been the most important."

Menninger (3) suggests evidence of the relation between the emotional life and sterility in the numerous reported cases in which reorganization of the psychic life results in pregnancies ten, fifteen and even twenty years after marriage.

Again, Deutsch (2) says that it is possible that psychogenic sterility has its origin in the emotionally disturbed course of the sexual act.

A number of explanations have been offered to account for the disturbed physiologic process in failure to conceive, with Sellheim appearing to be among those most frequently quoted. Menninger (3), in discussing the unconscious repudiation of femininity in women states that Sellheim assumes "... that the emotional factors are reflected in an overaction of the ovaries resulting in a premature maturation of the follicles, such that the ova are discharged which are not yet ready for fertilization." With decrease of the disturbing psychic causes, there is decrease in the pathological (emotional) stimulation of the ovary, thereby allowing it to discharge normal ova.

Anxiety as a Deterrent to Pregnancy

From the point of view of the emotional aspects of the problem, what becomes apparent in practically all discussions is that the most significant influencing factors are fear and anxiety at the prospect of becoming a mother. Anxiety or fear as factors in deterring pregnancy appear to be most clearly indicated in the explanations that are given to account for pregnancy after adoption.

Deutsch (2), in discussing the correction of earlier sterility through adoption, states that, "It must be assumed that in all cases of overcoming of sterility by adoption, the miraculous result is based upon the discharge of fear; of guilt feelings and of the neurotic belief, 'I cannot be a mother.'"

Orr (5) more specifically presents a detailed psychologic study of a woman who became pregnant shortly after the decision to adopt a child. In discussing the psychodynamics, Orr describes feelings of insecurity and a type of repudiation of femininity under pressure of strong unconscious anxiety which operated to preclude pregnancy.

It would seem that in instances of psychogenic sterlity where the woman has actually begun to take steps leading to adop-

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tion that these very steps may already reflect diminution of the disturbing emotional factors, so that it would be reasonable to expect possible pregnancy to follow.

The foregoing explanation for the not unfamiliar sequence—sterility-adoption-pregnancy—is one which seems at least apparent in the case which is described below.

Most of the literature which considers psychodynamics of sterility in the woman focuses strongly on feelings of inadequacy. In fact, a good deal of the available data suggests directly or indirectly that the disturbed behavior frequently reflects the woman's feeling about herself, namely, that she is still a little girl.

Orr (5), for example, in presenting analytic material with reference to Mrs. A., says that she could not have a child because she felt that she was not enough like a woman. Robbins (8), in discussing the psychological study of sterility in women, states that in many childless couples the wife is an extremely infantile individual. Duetsch (2), in her reference to the adoptive mother, raises among her questions on the problem of sterility, "Is she still so much a child that she cannot emotionally and unconsciously decide to assume the responsible role of mother?"

It seems to follow that in those instances where the woman sees herself as a child, she continues to respond in her present functioning to the same threat against her developing as a woman which she perceived when she actually was a child. This threat may be assumed to be the malevolent power of the maternal figure.

THE FUNCTION OF MAGIC THINKING IN ANXIETY

Piaget's findings (6, 7) in the field of genetic psychology have made perhaps the greatest contribution to an understanding of the psychic activities of the child. With a simplification which seems an injustice to Piaget's rich data I shall describe those of his concepts which I regard as most pertinent to this report.

In determining the development of intelligence Piaget groups the first stages under the heading of prelogic mental operations; the category of logical thinking he places last in development.

During the early years the child is unaware that his mind exists *per se* and that it functions in coping with reality. Thus he develops the belief that everything happens outside the mind. Projection is the characteristic mechanism of this phenomenon of "exteriorization."

Odier (4), who in his work attempts to bridge the gap between the psychoanalytic and genetic schools, uses Piaget's concepts and points up that the three mechanisms—projection, introjection and imitation—occur again and again in adult neurosis as in the child. Every thought originating in the self but attributed to others is considered as "coming from them."

Another characteristic of the prelogic stage is magic thinking which is intimately related to projection. Magic thinking seems to be associated with the early fears of the child. His feelings of danger, insecurity and helplessness incite him to maintain magic thinking, which serves as a protection and yet also at times as an action of destruction. The superstitious person, in his behavioral attempt to ward off what he perceives as danger, seems readily to verify the aforementioned operations in magic thinking.

In the prelogic stage the child tends to divide the world of reality into the "good" and the "bad." Whoever reassures and protects is good. He is liked by the child and, reciprocally, the child feels liked. Whoever threatens and frightens the child is wicked, disliked and felt in turn to dislike the child. In other words, the child's first concept of the world is that he is endlessly the object of the benevolent or malevolent thoughts and actions of others.

Odier reminds us that the functional unit, insecurity-anxiety, exists not only in childhood but at all ages. Whenever it appears it provokes a regression of both thought and affectivity to the magic level. In describing ego structure, Odier refers to "zone sectors."

He differentiates between the "progressive" sector and regressed areas. The activity of the former aims at adjustment to reality. According to Piaget (7), its principle is the assimilation of the data of reality. Emotions are adapted to reality and the psychic activity is logical.

As for the regressed sector, it is more appropriate to regard it as fixated at an infantile stage, *i.e.* the individual's ego at this point has not progressed. In regressed or fixated areas the individual interprets reality according to the emotions he experiences, and objective judgments become inaccessible to him.

CASE REPORT: A PROBLEM OF STERILITY

The ways in which an unevolved or so-called fixated sector can influence the functioning of an individual seem illustrated by the following data from the psychotherapeutic treatment of a young married woman. Her chief complaints were anxiety and inability to become pregnant. Therapy continued for a three-year period. There were approximately 250 sessions.

Mrs. C. was 25 years old when psychotherapy was undertaken. She was her parents' only child. Her husband was 30 years old. Mr. and Mrs. C. were married four years, and both were engaged in professional work. In addition to a full-time job on which she did well, Mrs. C. had the responsibility of the household which she also managed well in spite of constant concern in both situations that she was not doing well enough.

From the onset of marriage both husband and wife wanted children. Thus contraceptives had not been used. Gynecological examination of Mrs. C. revealed no basis for infertility. As to the husband, seminal fluid examination indicated that sperm count was somewhat under par.

HISTORY AND PSYCHODYNAMICS

Although there were other aspects of Mrs. C.'s personality which contributed to her difficulties and which were explored in therapy, the conspicuous thread which ran through her communications was the anxiety in relation to her perception of women and, coupled with this, her concept of herself. In most instances she saw women as malevolent and capable of hurting her either with criticism which was intolerable to her or, on a deeper level—as the analytic data revealed—with actual physical harm.

A good part of the anxiety seemed generated by her concept of herself as a child, weak and helpless when confronted with the powerful and strong adult. The aforementioned basis for Mrs. C.'s anxiety was confirmed by the psychologist's report of the Rorschach test, which was administered shortly after therapy started. This report states that, "At present, interpersonal relationships appear to have a painful connotation for Mrs. C., since they would expose her to the danger of being hurt." And again, "Mrs. C. seems to be questioning not only her ability to attract men, but also her adequacy for bearing children. There is preoccupation with wishing to have a child, opposed by the need to be a child herself. Mrs. C. sees her mother as over-protective and aggressive, giving her little opportunity to grow up and become independent; yet she also seems to gain some secondary gratification out of being 'the little girl' who can manipulate the environment in an indirect fashion, and can shirk responsibility by returning to immature phantasies."

From her early experiences with her mother Mrs. C. concluded that her mother wished to keep her a child. She said, "If I looked nice, it complimented her." Although as a child the patient was usually compliant, even wearing without fuss the home-made dresses which she hated, she felt that she never pleased her mother and was always in danger of inciting disapproval and rejection. Her father was described as quiet to the point where she felt she did not know him well. He enjoyed simple things and was easily satisfied.

Early anger seemed to find release in crying spells which persisted with the same in-

fantile expression when she was adult. On numerous occasions she would report to the therapist, "I cried and cried last night and it felt so good!" Crying was generally a private affair—made so perhaps because of fear of her own aggressive impulses. Conspicuous, in fact, throughout the course of therapy was the lack of overt affect to affectively toned experiences.

In her relation to her husband, on the other hand, Mrs. C. seemed to have much less need to deny her feelings. It seemed apparent, especially when she first came for treatment, that she perceived her husband somewhat in the role of the benevolent parent whose function it was to bolster her self-esteem and keep her secure. Whenever she felt that he had failed her, she would give free expression to her feelings, cry angrily and "tell him off." Odier (4) has pointed out that in such instances of aggression the vindictive person has regressed to an infantile level and feels and acts like a deceived child. Insecurity and dissatisfaction are identical.

In most relationships, however, Mrs. C.'s own hostility was denied or minimized by expressing it in a playful manner. For example, when I questioned her in response to her statement that she was afraid of what would happen to her in her visits to me, she laughed and said, "Well, maybe I'll turn into a little worm." It might be mentioned that especially in the early phases of therapy she reacted to the visit as if the therapist had imposed a demand and she had no alternative but to comply. There were such comments as, "I feel I will collapse when I come in," "I *have* to bring something and it's so difficult, so I just sink into a chair."

With her strong need not to arouse disapproval the patient seemed to have developed passive, manipulative mechanisms to gain sympathy by making others feel sorry for her. Invariably she would start the analytic session by telling of the exhausting train trip in, or her discomfort because of having to go out in wind, cold or rain. Her defensive need to be a child seems indicated in the following statement made when she was reviewing progress just prior to terminating therapy. "I really resented it. You wouldn't let me be a child and I had to give up the ways I figured out to be a little child and have women like me."

Her strong desire, however, to develop feelings of adequacy as opposed to her need to feel a child seems reflected in such statements as, "I want someone to say, 'Don't give up. It (therapy) is really worthwhile. It's not as impossible as it seems.'" "I really don't want to change yet I feel I should."

THE MATERNAL FIGURE PERCEIVED AS MALEVOLENT

Her perception of her mother as angry and destructive became evident not only from Mrs. C.'s direct references to her mother, but also from what was communicated in her transferred feelings to the therapist.

In an earlier paper (1) the writer attempted to demonstrate that perceiving takes place in a "tuned organism" and that the individual limits his perception to what is affectively meaningful to him at the time. Because of Mrs. C.'s early experiences she tended to see all women as more or less threatening and anxiety provoking. Consequently she tended to overreact in her relations with women at work as well as in social situations. For example, she would remark that, "She knocked me off my feet!" (this in response to an older woman's apparently polite correction of Mrs. C.'s comment on the ingredients of liqueurs), or, "She's so smart! She is always right!"

Dreams were frequently communicated by Mrs. C. This occurred particularly in the early phases of therapy, when she directly expressed fear of the therapist. She said, as a matter of fact, "I don't mind dreams. They are apart from me—like talking of someone else."

In his work on prelogic thinking Piaget

(7) describes dream development. In the first stage (5–8 years) the child believes that the dream comes from the exterior and remains exterior to the mind. Mrs. C.'s feelings about her dreams seem in large degree consistent with Piaget's first stage in dream development.

When Mrs. C. first came she reported recurring dreams of long standing from which she would awaken "scared to death" and "paralyzed with fright." Only fragments were recalled but all were concerned with fear of physical injury or destruction by a person or uncontrollable elements such as, in several instances, onrushing waters.

In her early relation to me Mrs. C. frequently saw the therapist in her dreams either in increased size or in oversized surroundings. Thus, in one dream I sat resplendent in a tremendous gold parlor. Mrs. C. sat huddled in the corner of a huge gold couch. Odier (4) discusses the "macroscopic phenomenon and the giant theme," and points up that the all-powerful giant is a symbol of powerlessness and thus a malevolent symbol. "Behind its immensity, the macroscopic image hides innumerable unpleasant memories and traumatic experiences which are at the basis of primary anxiety." In other dreams the therapist appeared as a wizened old woman, but witchlike, and so to be feared and avoided.

Avoidance, in fact, was a characteristic defense of this patient. She said repeatedly that she could not cope with women in authority. The inability of the ego to retain its identity before persons of prestige or authority has been described by Odier. He says that it is as if the regressed sector invades and replaces the ego and silences all its functions and faculties. "In an adult, this unconditional submission indicates a sort of mystical concept of parental authority which leads to abdication of the will and loss of the liberty of opinion, in one word, of autonomy, on the altars of that blindly venerated Being, 'who is always right.'"

Her fear of unconditional submission to the "malevolent being" was conspicuous, in a greater or lesser degree, in Mrs. C.'s communications throughout the course of psychotherapy. She would say, "I worked so hard to defend my opinion—not be be persuaded into anything I didn't want to do." Again, "I feel her (mother's) suggestion is good. She's superior and in charge." And again, "I always try to keep mother from being angry. The family is devoted to it." (At this point the patient laughed.) In still another session she said, "Terror strikes me when she speaks of being ill. I run before I'm trapped," (*i.e.* before attending her mother in illness).

On the other hand, any kind of assertion was usually followed by feelings of guilt and anxiety. Guilt occurred when, at the age of 20, in seeming emotional rebellion, Mrs. C. left home and came East in an attempt to achieve growth and independence.

One aspect of Mrs. C.'s avoidance was her secretiveness. She told me, "I love to keep secrets—to cherish them." Her reasoning was, "If it is pleasant, then it is not as pleasant if I share it. If it is unpleasant, then I'm afraid of the other's reaction to it." Thus, she couldn't tell her friends at college of her dates; nor her mother, until necessary, of arrangements for her coming marriage. And, most of all, in spite of progress which appeared to have influenced ability to conceive, Mrs. C. was reluctant to tell either her mother or the therapist when she became pregnant.

Nevertheless there was diminution of her fear in relation to me, and to women in general, and there were instances when she spoke of it. For example, in the session prior to the second summer vacation she said, "I'm not relieved with this vacation. Last year I was too afraid to depend on you. Now I'm willing to be dependent."

ACKNOWLEDGMENT OF FEMININITY AND PREGNANCY

About 18 months after therapy started, when there seemed considerable reduction

in the anxiety which had forced her first to come for help, the patient began to talk of plans to reduce the time which she devoted to her professional work. She said that she wanted to be a housewife, "to cook and iron and to enjoy taking things easy; to stay at home and care for children." Along with these plans she reported feelings of being more sure of herself—not so helpless; and she referred to earlier thoughts of adopting a child.

Her plans to adopt a child came increasingly to the fore. It should be mentioned here that up until this time there was a good deal of preoccupation with the wish to bear a child. With the first signs of menstruation each month there was renewed disappointment and complaints which at times were directed against her husband, but more frequently against herself and her inadequacies. The following comments reflect her feelings. "The period started. What's the use! They say plenty of women are pregnant yet have periods. There's no hope until next month." Again, "Something is wrong. I'm not working right to have a baby." And another time, "I feel that I do conceive. It really is a baby, but I can't have it. The period starts. I feel I had it, and then lose it."

As Mrs. C. progressed further in the direction of developing acceptance of her role and potentials as a woman—"more wifely," as she expressed it—and as her plans became more specific, it seemed that she again perceived the therapist as a threatening figure. And in her attempt to defend herself she became more resistant to the therapy and began to talk of terminating the treatment. She said, "In my mind, I say it is important, beneficial; but I don't really feel that way." At another time she said, "I don't want to find out anymore. I don't know why I'm doing it."

Mrs. C. did not terminate the treatment, however. The following chronology seems to point to the reasons why she continued:

January 15: Mrs. C. told me that she had applied to a child placement agency. She also made a request to have her days at work reduced from five to three. (In this treatment session she expressed fear that she might be offered a handicapped child).

January 17: The patient announced that her mother was going abroad for a few weeks. (Significantly, Mrs. C. did not say that her father was going with the mother.)

April 19: She reported that her mother had left. (Mrs. C. said, "I shipped her off in grand style!")

April 29: The patient related that she received a letter from the placement agency and was notified that the social worker would shortly make a home visit.

May 13: Mrs. C. said that her mother was coming home soon. (In this session she said, "I don't know what's the matter. I was sad this morning—all day. I'm unhappy regarding everything.")

May 23: The patient's opening statement was, "I think I'm pregnant. I'm late in my menses." She said that she intended to notify the agency of the suspected pregnancy; for they had indicated that a baby might be available for placement very soon. She added, "I have the feeling now, if it's not mine, I'll have no one's." (In this session she said, "I really didn't want to come. It's unheard of, but I have the feeling if I tell it (the pregnancy), it will go away.")

June 17: Mrs. C. reported that she had visited her gynecologist and that her pregnancy was confirmed.

The data suggest that diminution of Mrs. C.'s anxiety enabled her to conceive. As psychotherapy progressed, there were indications of some changes in self-percept and her perception of others. For example, shortly after her mother returned, on the occasion of a visit from her, Mrs. C. had these thoughts: While she and her mother prepared dinner

Mrs. C. thought, "She's not so good. She's not so perfect." She added, "I do it better." In communicating this to me, Mrs. C. said, "You know, I feel kindlier toward her."

But along with progress and instances where she did not give up to mother "who knows best," the interview material also indicates that Mrs. C. continued with feelings of being a little girl, and with her magic thinking.

The evidence is that Mrs. C. conceived when her mother was out of the country; although she probably would have conceived anyway, since the readiness to adopt seems to reflect some readiness to become a mother. Too, she was even more reluctant to tell her mother than she was to tell the therapist of her pregnancy. When she finally did tell her mother, and her mother suggested that Mrs. C. give up her work altogether during her pregnancy, Mrs. C. said, "I'm afraid something will happen—that I will lose the baby if I don't do what she says." She stopped working shortly after this.

Odier, in discussing nightmares, points up that as a rule dream thinking entrusts the morbid and destructive role to some omnipotent person. Odier refers to the magic power of malevolent representations which present the mind with images of disasters and catastrophies. "The subject behaves as though the imagined misfortune had really happened or will soon happen with inexorable certainty. Be the catastrophe a fact or only a threat, the anxiety is as intense."

In the period from the time Mrs. C. suspected pregnancy until the time that it was confirmed she reported very disturbing dreams from which she would wake up "frantic." Two significant dreams were reported in two different therapy sessions. The felt destructiveness of the omnipotent maternal figure (beautician and saleswoman) in response to Mrs. C.'s expression of her femininity, as well as Mrs. C.'s feelings of helplessness and inadequacy seem important manifest elements in the dreams.

The patient began one meeting by saying, "I am having the worst dreams—of being held down and I can't move and I wake up frantic—Tuesday and again today. I dreamed I was washing my hair. Something happened to the water so that I couldn't rinse it. I was furious. I thought in the dream, I'm like a child—a different hair-do—bangs and long hair. I went into another house to rinse my hair. There was a woman beautician who was going to rinse it, but she got hold of me and wouldn't let go. I screamed for help. Finally I got away."

The second dream was reported as follows. "I went to a dress shop. It was exclusive. My mother had gone there before. I went two times. The first time no one was in the store and the salsewoman was helpful. The next time my child was with me—a little girl—just able to walk. Such a lovely child! I went in and the saleswoman was not quite as attentive. There were other people there. I went to a dressing room a long way from the front of the shop. Then I couldn't find my little girl. I knew that she was there, but I couldn't see her. Then I found her but she was so little—like a ten-cent store doll!"

Mrs. C. continued in psychotherapy until the day before she gave birth. She said that if she terminated treatment before the birth, she would feel that she had "stopped in the middle." She also said, "I'll get everything out of it by December" (the expected month for the birth of her child). She now no longer complained, as she had previously, about the hardships connected with the therapy. In contrast, her manner was one of complete obedience. It appeared that in her pregnancy she now wanted protection through the power with which in her magic thinking she had endowed the therapist. When I questioned her about this, she said, "There's something to it. I feel that coming will makes things go right."

Mrs. C.'s pregnancy was a most healthy one. She seemed to enjoy it for its own sake perhaps as well as, if not more than, for the sake of the child. According to her report, she felt "not excited, but peaceful and contented."

SUMMARY

This report deals with psychogenic sterility in women. It approaches the problem from the point of view that an important factor in failure to conceive is anxiety in response to the woman's perception both of herself as a child and of the maternal figure as having malevolent power.

Piaget's concepts regarding the development of psychic activities are briefly reviewed and magic thinking, as an important characteristic of the prelogic stage in mental operations, is described.

It is suggested that the functional unit, insecurity-anxiety, exists not only in childhood but at all ages, and whenever it appears it provokes regression of thought and affectivity to the magic level.

More specifically, the paper deals with the phenomenon of pregnancy after the decision to adopt. In instances where the woman has taken steps toward adoption, the move to adopt itself reflects diminution of the emotional factors which caused the inability to conceive.

The case of a young married woman who became pregnant after decision to adopt a child is presented. The course of her psychotherapy is briefly described. The emphasis is upon her anxiety in relation to women in roles of authority, and upon the ways in which she employed prelogic magic thinking.

The materials of this case further demonstrate how prelogic or infantile thinking can occur in an individual whose psychic activities are in numerous respects on a mature level. The patient under discussion had superior intelligence, professional training and experience, and in many ways functioned quite adequately.

A number of writers concerned with the psychogenic aspects of sterility have indicated the lack of reported case studies from the psychological point of view. It is hoped that the data presented in this paper will contribute toward a better understanding of the emotional dynamics involved in the problem of sterility as well as in the phenomenon of pregnancy after decision to adopt.

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THE EFFECT OF LSD ON THE ASSOCIATIVE PROCESSES

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Although lysergic acid diethylamide (LSD) has been widely hailed as an important experimental tool in the investigation of the so-called functional psychoses, the psychological nature of the LSD "model psychosis" remains shrouded in mystery. Different workers hold sharply conflicting views concerning its possible relation to endogenous psychotic disorders, and even such crucial problems as the relationship of dose to LSD response and the influence of the subject's personality on his reaction to the drug have received little systematic attention.

An interdisciplinary research team at the Psychiatric Institute of the University of Maryland has been studying some of these important issues. In a recent paper, two of the authors have attempted to show to what extent the development of paranoid reactions in LSD subjects may depend upon certain very specific personality traits, and how this knowledge can help in predicting which subjects are most likely to develop such reactions (1).

It is clear that the typical LSD subject suffers impairment of a number of ego functions. Perceptual distortions are frequent, the ability to concentrate is affected, there are strange feelings of depersonalization, etc. Up to now, however, there have been relatively few attempts to compare systematically the responses of LSD subjects with those of normal controls and psychiatric patients on psychological tests specifically designed to assess ego functioning. This paper describes an attempt to attack this problem by administering the word association test (WAT) used by Rapaport, Gill, and Schafer (2) to 25 LSD subjects and an equal number of controls. In addition to comparing the responses of these two groups with each other, we shall attempt to compare the results of the LSD subjects with the schizophrenic, depressive, and neurotic patients and the control subjects studied by Rapaport *et al.*, keeping in mind, of course, that the groups were not equated for such critical factors as age, sex, and intelligence. Eventually, we hope to collect data on a sufficient number of schizophrenics to make a more rigorous comparison.

Before presenting the results of the experiment, a brief description of the WAT is in order. The test consists of two parts: in the first part, the subject is instructed to respond quickly with the first word that comes to his mind after hearing each of 60 stimulus-words. The examiner records and times the responses. In the second part of the test, the words are read again and the subject is asked to give the same responses that he gave the first time; all reproduction failures as well as delayed reaction times are noted.

In scoring the reactions, an adequate response is considered to be one which is related to the stimulus in a conventional way and which tends to be at the same conceptual level, *e.g., table-chair, dog-cat,* etc. Pathological responses vary from serious ones such as blocking, repetition of the stimulus, and clang associations to relatively minor deviations such as the use of proper nouns, self-references, *e.g., doctor-my father,* and phrase completions, *e.g., lampshade.*

In treating the data, we have followed,

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for purposes of comparison, the example of Rapaport *et al.* in making the following distinctions:

1) Responses to traumatic vs. those to nontraumatic stimuli. Of the 60 stimuli, 20 are considered to be "traumatic". They include such words as *breast*, *masturbate* and *mother*, whereas the nontraumatic stimuli consist of more neutral words, as *chair*, *screen* and *farm*.

2) Serious vs. minor deviations (examples of both have been given above).

3) Close vs. distant reactions. In order to understand this distinction it is necessary to outline the conception of the associative process offered by Rapaport *et al.* They regard this process as having two phases: an analytic phase, in which the stimulus is "broken down" into its subjective components, and a synthetic phase, in which an acceptable response is "built up" from the thoughts or images aroused by the stimulus.

Close reactions are believed to occur because of difficulties in the analytic phase. The associations do not seem to depart sufficiently from the stimuli and tend either to complete or to define the stimulus words. The more pathological reactions in this category include definitions, clang associations and repetitions.

Distant reactions are believed to be due to difficulties in the synthetic phase. There appears to be little or on connection, conceptually or otherwise, between the stimulus and the response, *e.g.*, *daughter-village*.

METHOD

Because individuals vary so greatly in their reactions to LSD, it is highly desirable that whenever possible subjects should act as their own controls. The experiment was originally designed in this way, but pilot studies made it clear that there is a marked "practice" effect when the WAT is administered to the same subject more than once. Subjects tend to have more popular responses and fewer association disturbances on the second testing, and, in order to investigate this effect, a separate study was undertaken, the results of which will soon be ready for publication.

In the present study, 50 young male adult volunteers were screened, by means of psychiatric interviews and psychological tests, in order to rule out serious psychopathology. The subjects were divided at random into two groups of equal size, one of which received 2 gamma/kilo LSD orally. One and a half hours after the drug was given, the WAT was administered. The subjects in the second group acted as controls. Each test record was scored by two judges and the overall percentage of scoring agreements for the 3,000 responses was 91.0 per cent (81.8 per cent excluding popular reactions, for which the scoring is objective).

RESULTS

Popular Reactions. The "popular reaction-words" listed by Rapaport *et al.* are those given by at least 10 of their 151 clinical and control cases. Although our records indicate differences in the comparative frequencies of certain adequate responses, we have, nevertheless, followed their list for purposes of comparison. According to Rapaport *et al.*, the proportion of popular responses decreases with increasing psychopathology. Their figures for the mean percentage of popular reactions in the various groups tested were: schizophrenics and depressives, 43.2 per cent; neurotics, 52.9 per cent and controls, 60.0 per cent. In the present study the means are 56.8 per cent for the control group and 47.4 per cent for the LSD subjects. This difference is significant at the 0.01 level ($t = 3.35$). The LSD group falls about midway between the psychotic and neurotic groups studied by Rapaport *et al.*, but we do not attach much significance to this quantitative difference. In comparing the reactions of the LSD subjects to the clinical cases of Rapaport *et al.*, we shall be particularly concerned with qualitative differences, since the degree of change

is probably closely associated with the dose of LSD administered.

Traumatic and Nontraumatic Stimuli. The data for total association disturbances show a highly significant difference between the control and LSD groups (see Table 1). This overall difference, of course, was to be expected.

It is noteworthy that although the LSD group has a somewhat higher number of errors on the traumatic words than the control group, this difference is not significant, whereas the difference between the two groups in the number of abnormal responses to the nontraumatic words is highly significant. The data were checked to see whether this result might be due to the fact that some of the nontraumatic words had become "traumatic" under the conditions of the experiment, thus receiving a disproportionate share of pathological responses. The statistical analysis showed that this was not the case.

Rapaport *et al.* found that in both their control and clinical groups the percentage of disturbances was significantly greater on the traumatic than on the nontraumatic stimulus words. Our results show a sharply contrasting picture. The control group does follow the general pattern described by Rapaport *et al.*, but the difference between the percentage of disturbances on traumatic and nontraumatic stimuli for the LSD subjects is not significant.

Reaction Time Disturbances. The data for reaction time reveal a significant difference between the LSD and control groups (see Table 2). It is interesting to note that once again the difference between the two groups is due primarily to their reactions to the nontraumatic stimuli. The difference in the mean reaction time on the traumatic words is not significant; for the nontraumatic words, the difference is significant. Looking at the data in another way, the LSD subjects show in their reaction times, as they do in their association disturbances, some tendency to abolish the differential response to traumatic and nontraumatic stimuli which is characteristic of the control group. Rapaport *et al.* found that both their clinical and control groups did react differentially to traumatic and nontraumatic stimuli.

TABLE 1

Association Disturbances on Traumatic and Nontraumatic Stimuli Under Control and Drug Conditions (For each group, N = 25)

Type of Stimulus	Control Mean	Drug Mean	*t*	P
Traumatic (20 words)	3.3 (16.4%)	4.2 (20.8%)	1.31	ns
Nontraumatic (40 words)	4.4 (11.1%)	8.1 (20.2%)	3.79	<.001
t	3.45	0.86		
P	<.01	ns		
All Stimuli	7.7	12.2	3.37	<.001

TABLE 2

Reaction Times on Traumatic and Nontraumatic Stimuli Under Control and Drug Conditions (For each group, N = 25)

Type of Stimulus	Control Mean	Drug Mean	*t*	P
Traumatic (20 words)	3.0″	3.2″	0.70	ns
Nontraumatic (40 words)	2.3″	2.7″	2.93	<.01
t	3.56	2.54		
P	<.01	<.05		
All Stimuli	2.4″	2.8″	2.50	<.05

TABLE 3

Serious and Minor Deviations Under Control and Drug Conditions (For each group, N = 25)

Type of Deviation	Control Mean	Drug Mean	*t*	P
Serious	2.4	6.2	3.21	<.01
Minor	5.3	6.0	0.77	ns

Serious and Minor Deviations. It may be of interest to note that the tendency to make serious deviations is significantly greater in the LSD group than among the controls (see Table 3). On the other hand, the difference between the two groups in the mean number of minor deviations is not significant. This parallels the finding of Rapaport

TABLE 4

Close and Distant Reactions Under Control and Drug Conditions (For each group, N = 25)

Type of Reaction	Control Mean	Drug Mean	*t*	P
Close	2.1	4.7	2.95	<.01
Distant	2.4	3.2	1.11	ns

TABLE 5

Serious and Minor Reproduction Disturbances Under Control and Drug Conditions (For each group, N = 25)

Type of Disturbance	Control Mean	Drug Mean	*t*	P
Serious	5.5	9.4	2.97	<.01
Minor	4.5	6.0	1.63	ns
All Disturbances	10.0	15.4	3.44	<.01

and his associates, that a relative increase in serious deviations accompanied an increase in psychopathology.

Close and Distant Reactions. According to Rapaport *et al.*, the incidence of both close and distant reactions was greater in their neurotic and psychotic groups than in their control group. However, they reported a significant difference in the relative increase of the two types of reactions in the various diagnostic categories. Thus a marked increase in close reactions was characteristic of depressive patients whereas schizophrenics tended to accumulate distant reactions. Neurotics, too, characteristically had a greater increase in distant reactions, although to a lesser extent than the schizophrenics.

The results of the present study are recorded in Table 4, which shows that the LSD subjects gave a considerably greater number of close reactions than the controls. This is not true of the distant reactions, where the number of errors, although greater in the LSD group, is not significantly so.

Reproduction Disturbances. Rapaport *et al.*, divide reproduction disturbances into two groups: serious deviations, which include unrelated false reproductions, failures to reproduce and long delays of correct reproductions; and minor deviations, which include related false reproductions, corrected false reproductions and partially correct reproductions. They found that the number of reproduction disturbances was proportionate to the degree of psychopathology, and that this was especially true for serious deviations.

Our results fully bear this out. Table 5 shows that in total reproduction disturbances, the LSD group significantly exceeds the control group. However, this difference is almost entirely in the category of serious deviations. In the case of minor deviations, the difference between the two groups is not significant.

DISCUSSION

To summarize the principal findings of the study: As compared with normals, LSD subjects make more errors, have fewer popular responses and react more slowly. In addition, close reactions predominate, as do serious deviations and the differential reaction to traumatic and nontraumatic stimuli is abolished.

In comparing these results with those for the clinical groups studied by Rapaport *et al.*, we see that the LSD responses form a pattern quite distinct from that of any of the endogenous disorders. In two major respects, the preponderance of close reactions and the abolition of the differential response to traumatic and nontraumatic stimuli, the LSD subjects differ from all the clinical groups. It is true that the depressive group of Rapaport and his co-workers also showed a great increase in close reactions, but this was accompanied by a substantial increase in distant reactions. In this connection, it is interesting to note that Woodrow and Lowell (3) administered a word association test to 1,000 children, aged 9–12, and found that there was a tendency for their subjects to complete or enlarge upon the idea conveyed by the stimulus rather than to give a related, parallel response.

How can we explain the puzzling tendency of the LSD subjects to react nondifferentially to traumatic and nontraumatic stimuli? The crux of the matter is that they make no more errors on traumatic words than do the controls, despite the fact that the overall responses prove that their associative processes are significantly disturbed. We know from their reactions that the words are heard and understood by the subjects and yet they have no more effect than the more neutral stimuli. We have numerous examples of how subjects under LSD actually responded more adequately to certain charged words than they did under nondrug conditions. One subject, for example, gave as a response to the stimulus word *penis* the association *peter* under the influence of LSD and *a man's organ* under control conditions. Another volunteer offered *sexual* as a response to *intercourse* under drug conditions and gave *affairs with a woman* in the control part of the experiment. In both these illustrations, the control responses are clearly inadequate by the standards of Rapaport *et al.*, since they are multiword definitions rather than conceptually equivalent, one-word associations. Under drug conditions the responses are better but in the first case, a vulgar word is used, and in the second case, what is probably a more emotionally charged word is used.

There has been a certain amount of speculation concerning the impact of LSD on the "repressive barrier," and certainly one would expect that any such effect would influence the way LSD subjects would react to charged and noncharged stimuli.

From the ego-psychological point of view, the conventional responses, which are given quickly and automatically, can be viewed as representatives of what Hartman calls the conflict-free area of the ego. In normal individuals, the great majority of nontraumatic stimuli can be handled in this automatic way without serious interference from unconscious influences. Traumatic stimuli are much more likely to impinge on conflictual areas and, therefore, to elicit slower, more deviant responses. In the case of neurotics and especially psychotic patients, the conflict-free area of the ego is narrowed, but, nevertheless, is still comparable to what we find in normal subjects. It is likely that LSD in hallucinogenic doses succeeds somehow in dissolving the boundaries between the autonomous and conflictual areas of the ego. Obviously, we have only placed an observed phenomenon in a convenient frame of reference, without attempting to answer the question of how this change in the ego comes about.

One final question which merits brief comment is the problem of dosage in LSD experiments. As was mentioned above, the degree of abnormality on any test using LSD subjects will tend to increase with dose. It has even been suggested that the LSD reaction changes qualitatively with increasing dose, and, if this should prove to be so, the conclusions drawn from the data of this study may have to be qualified. Up to now, however, no convincing evidence has been put forward to indicate that altering the dose of LSD will actually change the nature of the reaction in any significant way. Lowering the dose will bring the subject closer to normality, not to schizophrenia.

SUMMARY

1. The responses of 25 LSD subjects to the word association test employed by Rapaport, Gill and Schafer have been compared to those of a control group and to the responses given by groups of schizophrenic, depressive, and neurotic patients tested by Rapaport *et al.*

2. Our analysis shows that in the associative processes, at least, the LSD reaction does not closely approximate any of the principal "functional" psychiatric disorders.

3. Probably the most striking way in which the LSD reaction differs from all other conditions is the abolition of the differential response to traumatic and nontrau-

matic stimuli. We have attempted to place this phenomenon within the framework of modern ego-psychology theory.

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THYROTOXICOSIS AND ITS PSYCHOSOMATIC APPROACH[1]

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It is now generally accepted that many phenomena of emotional expression such as tremor, perspiration in fear, palpitation, diarrhoea, etc., point to a hyperactivity of the thyroid gland and correspond to the classical symptoms of Graves' disease. It is also well known that usually long before the onset of thyrotoxicosis, and often dating back to childhood, patients suffering from the disease display a picture of emotional and psychosexual maladjustment.

The purpose of the present paper is to describe the psychosomatic approach to the problem of thyrotoxicosis by presenting:

1. A review of the literature.
2. The physiopathology of the disease.
3. The psychosomatic observations which include the psychopathology and the psychodynamics of the syndrome.
4. The results of the writer's observations and research on thyrotoxicosis in Greece.

REVIEW OF THE LITERATURE

Cases of hyperthyroidism of emotional origin were observed as early as 1825 when Gallep Hillier Parry (26) of London described ten years prior to Graves' paper a "new malady which I had seen recently in five consecutive cases." All of them were attributed to emotional factors, fear in particular. Graves himself (12) devoted most of his classic monograph, published in 1835, to an attempt at establishing a causative relationship between hysteric conditions and hyperthyroidism.

Möbius (24), in 1886 was the first to point to the endocrine origin of the diseases of the thyroid (hyper- and hypothyroidism). Until his time hyperthyroidism was classified among neuroses.

Raymond Crawford (8) in his excellent dissertation, published in 1897, refers to Graves' disease as "a disorder of emotional origin."

It was Marañon (21), however, who not only attempted a systematic clinico-biological study of the disease based on 159 cases which he followed up himself, but also stated in his paper that in 48 out of his 159 cases (28 per cent) there was present during the time of the onset "an intense emotional upset."

Marañon made the carefully documented statement that "at least eight subjects" of his series were "perfectly normal physically and mentally prior to the onset of the disease." He also noted that Graves' disease more often followed "the long-continued reaction of depression rather than the short-timed emotional traumata," and stressed the etiological role which marital maladjustment seems to play in the process.

Bram (4) and Wallace (32) also pointed out, separately, that stressful emotional situations, either acute or chronic, may lead to hyperthyroid manifestations, while Gatting (11) was first to coin the term "Krieg Basedow" (war hyperthyroidism) during the Second World War, in which he saw some typical thyrotoxicoses.

Rahm (29), of Breslau, supports the view that sudden fright or fear may precipitate a typical Basedow symptomatology within a few hours, which rarely recedes from the scene, if there exists what he calls "a constitutional inferiority" of the endocrine-neuro-vegetative mechanisms regulating the thyroid function.

Hayman and Kessel (15), as quoted by

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Conrad, investigating the problem of relationships between neurovegetative imbalance and thyrotoxicosis, found that in almost all of the subjects examined in their series "an emotional trauma was found which directly or indirectly was related to the onset of the disease."

PHYSIOPATHOLOGY

Some of the clinical symptoms of thyrotoxicosis can be induced by the administration of excessive amounts of thyroid hormone and therefore can be considered the direct results of thyroid hyperfunction. Other symptoms are neurogenic or of emotional origin.

The neurovegetative regulation of the thyroid gland as well as the precise mechanism of its hyperfunction has not yet been fully established. However, the fact that the thyroid gland is enlarged and its activity increased during pregnancy is a further evidence indicating the role of the gland in the process of both growth and procreation. Brown (5) called the thyroid "the gland of creation."

Wittkower, Scheringer and Bay (1932), quoted by Wittkower (33) carried out a number of interesting experiments with regard to basal metabolism, the skin-condenser index (with Lueg), and the blood iodine content in patients with thyrotoxicosis.

It must be remembered in relation to the above that increased basal metabolism may be attributed either directly or indirectly to the stimulation of the sympathetic which in turn produces an increased activity of the thyro-adrenal apparatus and the hypothalamo-hypophyseal system, and that adrenal and thyroid hormones act uniformly in principle though there is a difference in their speed of reaction. The thyroid hormone acts slowly, more weakly and more persistently, whereas adrenalin acts quickly, temporarily and strongly.[3]

It is also now accepted that the increased secretion of the thyroid gland is due to the thyroid stimulating (thyrotropic) hormone of the anterior pituitary gland. The best understood mechanism in thyroid activity seems to be similar to that postulated by Selye and extended by Long and Mirsky as follows.

A variety of stresses: chemical, toxic, nervous and emotional, may activate the anterior pituitary gland either directly, through an effect on the hypothalamic area, or secondarily, through activation of the sympathetic-adrenal system. This is in accordance with Soffer's (30) observation that adrenalin (epinephrine) administration results in increased activity of thyrotropic hormone, and Uotila's (31) observation that cutting the stalk of the rat will prevent hypertrophy of thyroid gland which usually follows exposure to cold.

Harvier and Froment (14) and Delay, Gendrot and Renard (9) have, I believe, contributed to that position by their observation of coincidence of thyrotoxicosis and parkinsonism due to emotional experiences and upheavals during the last world war. They postulate that affectivity, hormonal cooperation and muscular tone are controlled and regulated by diencephalic centers and that stimulation of the diencephalo-hypothalamo-hypophyseal area through emotional and humoral percussions, might lead to a combined involvement of affective, muscular and hormonal expression as it becomes evident in the clinical coexistence of parkinsonism and thyrotoxicosis.

Electric convulsive therapy, on the other hand, applied to psychotics resulted in either thyrotoxicosis (Harvier and Froment, 14) or insipidus diabetes, hypertension, hyperglycemia etc., while some investigators noted favorable results after ECT

[3] On a phenomenological basis adrenal activity produces acute anxiety states whereas thyroid overactivity results in a chronic slow, anxiety-like situation. This lead Miles and Cobb (22) to publish an excellent paper in which they indicate the need to consider the possibility of a clinical combination of anxiety and thyrotoxicosis.

with parkinsonic syndromes of emotional origin. This, according to the aforementioned French authors, shows how "sensitive" the diencephalic nuclei are, particularly in subjects "emotionally labile."

PSYCHOSOMATIC OBSERVATIONS: PSYCHOPATHOLOGY AND PSYCHODYNAMICS

Numerous publications have dealt extensively with psychodynamics in thyrotoxicosis since Nolan Lewis (16) first was impressed by the prevalence of impregnation fantasies and the markedly incestuous fixation upon the father exhibited by hyperthyroid women, whereas the only man studied by him revealed homosexual cravings and resembled the women because of an observably inverted oedipal complex based on feminine identification.

Agnes Conrad (7) psychoanalyzed three women and was also impressed by their extreme dependence upon their mothers, their fear of losing affection and shelter, and by the stress of the burdens that are involved in assuming the maternal role and the resulting difficulty of making identification with the mother. She also found a statistically significant incidence of loss of the mother during early infancy and childhood. The male patients studied by her revealed an excessive and unusual attachment to and/or dependence upon their mothers.

Mittelman (23) and Lidz (17, 18) also observed unusual dependence upon a parental figure, usually the mother, through a continued sibling rivalry, in 60 and 15 patients respectively.

Lidz and Whitehorn (19) stated their conclusions as follows. "These studies of hyperthyroid patients have brought fairly consistent indication of a typical life situation, consisting of the disruption or threat of disruption of a devotedly dependent personal attachment, to which threat the vulnerable patient reacts in a deeply emotional way because such a dependency is required to fulfil a basic personality need."

Brown and Gildea (6) noted that their patients had an extreme feeling of insecurity, a strong sense of responsibility, and a tendency to control outward expression of emotions, and that any threat of their security either by prolonged strain or by sudden emotional shock could precipitate hyperthyroidism.

The Chicago group (Ham, Carmichael and Alexander, 13), in their investigations with thyrotoxic patients, confirmed the findings of previous investigators; particularly with reference to the significance of fear and anxiety, marked dependence upon parental figures, excessive insecurity and the defensive mechanism at work (namely in efforts toward assuming responsibility, achieving maturity, becoming self-sufficient and taking care of others).

Threats to security in infancy and early childhood appeared to these investigators to be the nucleus of the neurotic structure of thyrotoxic patients. Patients often handle this insecurity by turning to their parents for help. As their dependent needs are increasingly frustrated by fate and parental attitudes (loss of mother or father or both, parental rejection, etc.), they make a desperate attempt to identify themselves prematurely with one of the parental figures, usually with the mother.

This precocious identification is beyond their psychological and physiological capacities and results in a persisting struggle to master the anxiety and insecurity through a defensive pseudo self-reliance or "pseudomaturity." The constant struggle against anxiety is usually manifested through denial and a counterphobic attitude—a compulsive need to undertake those activities which are most feared.

Similar emotional contradiction appears in the compulsive urge to become pregnant in spite of fear of pregnancy, *i.e.*, the fear of death is mastered by giving birth to children or taking care of them. Thyrotoxic patients are full of sexual fantasies and the content of their dreams often focuses on death, ghosts, caskets, and dead persons.

The Chicago group also noted a strong repression of hostile impulses resulting from extreme dependency. The assumption of a mother-like, protective attitude towards younger siblings frequently represents either a compensated sibling rivalry or a gratification of the patient's own dependent needs, and also serves to expiate the guilt derived from rivalry.

Mandelbrote and Wittkower (20) and Dongier and Wittkower (10) came to conclusions similar to those of previous investigators, although in trying to establish a clear psychopathology of thyrotoxic patients, they appear to be more concrete and more objective. In their excellent paper on 25 thyrotoxic patients and an equal number of controls Mandelbrote and Wittkower summarize their findings as follows.

Concerning psychopathology they agree with Lewis in his opinion of an oedipal fixation, but they also note that regression in thyrotoxic patients continues to still earlier stages of psychosexual development. As an example they refer to the observation that excessive hunger and eating start often before the slightest sign of increased metabolism can be noted. In that sense the authors interpret thyrotoxicosis in psychoanalytical terms: "1) as a symbolic expression of oral impregnation fantasies; 2) as a symbolic expression of introjection of the ambivalent mother, and 3) as an unspecific affect concomitant of regressively released anxiety arising from the sources indicated." They cannot, of course, see anything specific in the personality profile of the subjects examined because similar features have been found in some other psychosomatic disorders too.

Wittkower and Mandelbrote also reached conclusions similar to those of earlier investigators with reference to the hostile dependent relationship to the mother, but their findings differed strikingly in some aspects from the results of Ham, Carmichael and Alexander.

Their patients did not come from larger families than those of the control cases, and the incidence of broken homes was equal in both groups. The number of children of the patients was also not so great as that in the series of the Chicago group and the number was somewhat smaller in the thyrotoxic than in the control group. The thyrotoxic patients, however, were significantly more neurotic than the control group and their sexual adjustment was also much inferior. Anxiety, subnormal self-assertion and depression were also found to statistically greater degree among the thyrotoxic patients.

Dongier and Wittkower, in trying to establish evidence of a relationship between personality structure and thyrotoxicosis, summarize their conclusions with regard to psychopathology, psychodynamics and the "criteria" arising from their study as follows.

The basic need of these patients is for more love than they can get. Their response to being frustrated is aggressive in nature and is tantamount to death wishes. Regressive revival of fantasies and impulses of this nature give rise to feelings of anxiety and to feelings of guilt which may be ill defined and wrongly placed. To ward off anxiety—and in keeping with their basic need—they may display an overdependent relationship to their mother or, as a secondary defense, they may ostentatiously turn away from their mother and try to find a solution in premature striving for self-sufficiency. This ego defense is feeble. As it fails to be effective—and in fact leads to further estrangement—patients may revert to a passively dependent appeasing attitude in the hope of winning back affection.

Patients in whom the appeasing attitude prevails make constant efforts to win the approval of their mother. They may displace their efforts from their mother to a suitable mother substitute to whom they bind themselves very closely. Or they may lavishly shower affection on others, expect-

ing unconsciously that in return they will get as much affection as they give, if not more. Strange though it may appear, their children often serve as such mother substitutes. Despite many conflicts and fears in relation to childbirth, these patients often have an extreme longing for children, based partly on their desire for restitution and partly on the need to have someone with them. While the child is small the patient can feel secure because it is bound to her by its dependency needs and state of helplessness; but when the child seeks independence, the mother reacts with fear (of loss of love) and anger (at being deserted).

Reaction formations against the revived hostile feelings lead to anxious over-concern lest harm befall the needed love object. The theme of warding off the loss of a person they need, lest they be isolated, runs through their lives.

These patients have an intense fear of being left alone and unattended. As a result of their destructive impulses and fantasies this fear is effectively camouflaged in those patients who are unable to accept any situation of dependency. They display early in life a premature striving for self-sufficiency and are apt afterwards to repudiate their feminine role in view of its passive connotation dependency. Hidden behind the hustle and bustle of their activities and their constant emphasis on independence and self-sufficiency lurks the same out-dated cry for maternal care and lavish affection that moves those who reveal their needs more patently.

Male patients tend to have similar personality structures. They usually display signs of feminine identification and, in some, the wish to assume the maternal role is conscious.

The question may be raised: Are there any differences in thyroid function, as evidenced by the curve of biological decay, between individuals handling their basic emotional conflicts in a manned similar to that observed in thyrotoxic patients, and individuals who have different psychological defense mechanism?

The "criteria" of Dongier *et al.* are: 1) early premature striving for independence; 2) denial of hostility; 3) undoing of hostile impulses by overconcern regarding the needed and ambivalently regarded object; 4) a tendency to gain affection by a compulsive "doing for others"; 5) desire and need for children (conflicting with fears of pregnancy and child-bearing); 6) feminine identification in male patients; 7) feebleness of defenses which makes these individuals anxiety prone.

The writer's observations derive from a series of eleven female thyrotoxic patients seen in Greece and do not differ at all from those mentioned above. The investigation was carried out as follows (27, 28).

MATERIAL AND METHOD

The subjects were a group of eleven thyrotoxic females out of a total of 105 thyrotoxic patients then attending the neuropsychiatric outpatient clinic of the *Army Pension Fund Hospital* of Athens, Greece. As there were no facilities for radioactive-iodine uptake studies at that time in my country, in all these cases the clinical diagnosis of thyrotoxicosis was substantiated by basal metabolic rate and cholesterol determination.

In all, 28 patients were interviewed; some while acutely hyperthyroid, most during their intermediate states, and a few after they had become euthyroid following the administration of antithyroid drugs.

From these 28 patients was obtained a series of eleven cases, all females. The material therefore can be considered as selected in the sense that all cases were subjects eventually found to have a severe form of thyrotoxicosis both from the clinical and the laboratory standpoint. Of these eleven cases; three had a basal metabolism ranging between plus 30 per cent to plus 40 per cent, four between plus 40 per cent to plus

50 per cent, two between plus 50 per cent to plus 55 per cent, one had a plus 56 per cent B.M.R., and one a plus 58 per cent.

The cholesterol values ranging between 1.60 mgr. per cent up to 2.60 per cent mgr. The psychiatric investigation consisted of psychoanalytically oriented interviews carried out by the writer. Each patient was seen in successive interviews of a standard period (45–50 minutes each), for at least five interviews, and the material of the interviews was recorded. Relatives or friends were interviewed in only two cases. Apart from their anamnestic interviews the patients were seen regularly in treatment for between two and three years at a two to three months' interval.

Eleven control subjects were collected at random from the medical out-patient department of the hospital, were matched as to age, sex, and social and economic status, and were interviewed on the same schedule as the thyrotoxic patients

Psychological tests were administered and interpreted by a staff psychologist. The Wechsler-Bellevue Intelligence Test, the Rorschach, Thematic Apperception Test and the Figure Drawing Test were used. All eleven patients and ten of the controls were given the full battery of the tests, but for technical reasons the Rorschach was given to four subjects only.

The average duration of the testing was two to three hours. In addition, all eleven patients as well as the controls had an electroencephalographic study. All subjects had EEG records within the normal pattern.

CASE HISTORIES

The condensed case histories below present the general life situation of the patient immediately prior to the onset of the illness, and emphasize one or more characteristic features of the personality involved, from a dynamic aspect.

CASE 1. The patient, a 55 year old married Greek female, complained of having thyrotoxic symptoms since 1944, "just after the Germans had put me in front of the wall and threatened to shoot me." She was saved by the approaching partisans who started in their turn to torture her for her husband's pro-British attitude at that time. The patient comes from sound parental stock and a large family, the care of which she shared with her mother from her adolescence onward. She herself wanted to raise a big family and liked the idea of having "as many daughters as possible," because "girls are easily handled as compared, with boys; so my mother used to say." Actually the patient now has three daughters, one of whom is the seventh patient in this series.

CASE 2. This is a 46 year old widow, who lived in the rural areas of Northern Greece. Her only son was, and still is, a regular army officer whose relatives and friends in his native place were a valuable target for the rebels. The patient herself had a narrow escape when her house was set on fire by bandits in 1948. Sometime later she developed acute symptoms of thyrotoxicosis.

CASE 3. Miss E. M., a Jewish spinster of 40, is the only member of a family of seven who survived the German terrorism in Salonica, Greece. She was devoted to her "gentle" parents and used to be the mother's substitute in taking care of the younger members of the family, two girls and two boys, all of whom were sent by the enemy to Germany, never to return. The patient managed to escape and reached Athens in 1944, with no resources and no relatives on whom to depend. After the liberation, she spent months on inquiries only to learn through the Red Cross that her entire family had been exterminated in concentration camps in Germany. This gave the patient a feeling of "loneliness and insecurity" and shortly afterward the symptoms of thyrotoxicosis made their appearance.

CASE 4. A 26 year old single woman, this patient is one of seven siblings surviving from a total of 20. Her mother, who died recently in her late fifties, is described by the patient as a "loving and devoted mother" who wanted to have lots of children to care for. The father is a retired army officer now engaged in private business. He is a good humored, easy-going, simple type of personality whose main contribution to his family was, evidently, the financial one only. The dominant parent seemed to be "the loving and devoted mother." The patient, who is the only female among the siblings, started to share her mother's duties at thirteen years of age, soon after she had her menarche, and was told by the mother that "this obliged her to play the feminine role." She is consciously envious of the boys' privileges but likes helping them in their striving for social prestige and success. Three years ago, after her mother died, the patient met a boy two years her junior with whom she had her first love affair. However, she

never felt happy and always considered what the mother would say if she were alive and could see her only daughter neglecting "the boys" and the household for the love of a younger partner. The patient had several dreams about death and cemeteries and once she had a phantasy that her dead mother was lying on her own (the patient's) bed, which was like a coffin.

CASE 5. This patient, a 23 year old teacher at an elementary public school in Piraeus, Greece, developed thyrotoxicosis soon after she was ordered by the Ministry of Education to report in January 1948 to the North Greece Educational area. The situation she found there was extremely dangerous and insecure. The patient is the only child of an elderly couple. The father is a retired army officer, very fond of the patient, and the mother a retired school-teacher herself. The patient used to take care of her old parents herself and felt happy and satisfied when she managed adequately to fulfill both her home and school duties. She was very active, closely attached to "father rather to mother," as she puts it, but used to copy her mother who was "a competent figure to be respectfully imitated." She related some dreams with illustrative material about death. The following is one of them. "An old woman with gray hair was killed by the rebels somewhere in North Greece." Identification with the mother is quite evident in the dream. The patient finally resigned from her post and returned to the parents. Two months later she lost her "dear and beloved" mother. Then she began complaining of thyrotoxic symptoms.

CASE 6. This patient, a 28 year old woman, had always had feelings of being rejected by her mother, whom she describes as a domineering, self-centered, stubborn and demanding figure "with no affection at all." She is the second among four siblings. The father died when the patient was six years old. She was married in her twenties to a man of 28 years, in spite of the mother's wish that she marry "a well established gentleman" 20 years her senior. She has two daughters and plans to have one more child, "perhaps a boy." Her interest in marriage came as a result of her wish to feel independent of her mother and have her own family and children to care for. The young husband proved to be a very cooperative one, "an excellent type of man" who encouraged his wife in her attempts to become a model mother. The patient and her husband were seriously considering the possibility of a third child and talked it over with the mother, who stubbornly rejected the idea. Arguments ensued for a period of months and it was during this time that the disease onset occurred.

CASE 7. This 15 year old Greek girl, daughter of the first patient in this series, is described by her mother as "a fine little housekeeper" who takes over her duties whenever the mother becomes ill or is working outside the home. The patient has not yet menstruated, is of an asthenic physique and appears proud when the mother praises her in front of the doctor. She pays, however, no attention at all to the anxiety with which the mother relates the story of her illness. The girl was extremely upset and terrified when she learned of plans to send her to join the father, now living in the United States. She then commenced to become thyrotoxic. "I guess the girl does not like the idea of leaving us. I'm going to miss her, Doctor. She was my right hand."

CASE 8. This is a 22 year old woman, married at 19 to a captain in the Greek Army, 6 years her senior, who was ordered to Korea on active service soon after their marriage. The patient is the only child of a well known and well established Greek couple who both died the year prior to her marriage. The patient made desperate attempts, through social and political acquaintances, to follow her husband to Korea though he was completely unaware of her unsuccessful efforts. She then started to complain of dizziness, hand tremor, sleeplessness and a sense of fatigue. However, she stayed home "in a new, strange environment" with her old, widowed "vicious" mother-in-law and her six in-laws all males. At first she liked the idea of assuming responsibility in the home, as she enjoyed "taking care of others, a habit I had since my school years." Gradually the mother-in-law forced the patient to shoulder all the responsibilities and presented her with more assignments and more difficulties, until the patient had a breakdown "just the very day my doctor told me I was going to be a mother." "I craved a child," the patient says, "though I knew it was one more person to care for." The condition became worse when the mother-in-law "ordered" the patient to stop playing the piano, the only entertainment she had, and later, when the bad news came from a base hospital in Tokyo that her husband had been seriously wounded, the patient came to me with a thyrotoxicosis.

CASE 9. This is a young woman of 22, who first presented herself to the physician with a feeling of nervousness and a sense of globus in her throat. She comes from Peloponnesus, a rustic area of South Greece, and is the only girl in a family with six other siblings. The mother had been sick for years and was always anxious over her childrens' health. "She never had a smile for us ... but she always was concerned and anxious for us," the patient said. Some weeks prior to the liberation of Greece her younger brother had been taken away by the Germans as a hostage, and never returned. The patient, who had always felt competitive with that particular brother on a conscious level, had

also felt guilty after his arrest, and did her best to find out his whereabouts. In that same year (1945), the mother died in a provincial hospital from pneumonia while the father started to drink in excess and fell ill. The patient began to feel desperate and hopeless but managed to take care of the sick father, the boys and the house. She herself, being the only woman left, felt forced by circumstances to take over responsibility which she "always did dislike." Two years later the Greek Red Cross reported the news of her brother's death and it was at that time that I first saw the patient.

CASE 10. This is a 34 year old widowed female patient, the third child among four siblings. As far as she can remember, the patient has been troubled by feelings of self-consciousness and inadequacy. She has also been afraid of authoritative figures, of strange environment and strange people. The mother used to over-protect her and to show favor overtly for the patient who was for the mother "her best daughter." The onset of her symptoms was related to specific situations clarified by the patient herself. While engaged she had intercourse with her fiancé. The experience was painful, and she began to feel guilt and shame. It was impossible for her to face her mother and confess "her secret." But before her marriage she finally confided in both parents, whose attitudes were both humiliating and punitive. At that particular time she noticed a slight tremor of her hands, palpitations and insomnia, and the swelling of her thyroid. While the symptoms were at their peak her husband was killed in an accident and the patient felt desperate. She bore the experience with courage however, and felt relieved somehow "just after the funeral service was over." The idea that she would now be free to make her own plans for the future was a pleasant one and gave her a feeling of well being.

CASE 11. This patient is a single woman of 21, the only child of her mother's second marriage. Her two half-brothers, who are four and six years her senior, have never shown her any affection. In spite of her mother's instructions the boys tried to humiliate the patient in all circumstances, while nevertheless expressing concern for her. At the age of 18 she became anxious at the beginning of her first love affair "lest the partner be like her half-brothers." Consequently she turned down the boy's proposal on the grounds that "she was too young to leave her mother alone." She enjoyed the idea of being married only to have children "though I crave an only child; when you have an only child you love it more." When her mother fell ill three years ago the patient took over the household and the responsibility of caring for her half-brothers. Her thyrotoxicosis coincided with her marriage which added to the existing burden of responsibilities. The patient still bites her nails, a habit she has had since she was a child.

DISCUSSION

Almost all of these patients had been exposed to early insecurity during their psychosexual development. This became evident in, and has been confirmed by, their psychological assessment and the psychiatric evaluation.

This insecurity seems to have reached its climax during a collectively critical period of the existence of Greece as a nation, during World War II, the Italian and German occupation, and the civil war which ensued, a period of time which covers almost ten years. At that time most of these thyrotoxic patients were restricted to their houses and were obliged to take care of their families and homes. They were therefore forced by circumstances to relive and re-experience in a continuous way what they were consciously longing for and afraid of; namely, to take responsibility, to replace the mother, to protect younger siblings, etc.

This appears to have been a defensive "pseudo-maturity," easily broken down when any of them was confronted with even the simplest emotional conflict or actual emotional experience. This became most evident among females and supports the view that psychosomatic integration is more apt to develop regressive phenomena in women because of the existing psychophysiological alterations to which the female individuals are "normally" subjected during their life (menstruation, pregnancies, climacterium, etc.).

Death fears and phobias and the ensuing defensive anxiety occurred in almost all these patients as a result of external circumstance. Anxiety was certainly a dominant sensation among the peoples of occupied countries, so that death fear was secondary to anxiety occasioned by repressed instinctual drives.

It is of some importance, however, to

mention here that many men were able to express their aggressive impulses actively and to turn them against the enemy. Thus they gave way to their defensive anxiety and compensated for the deep-seated death phobia. This may explain, at least in part, the low incidence of thyrotoxicosis in males in all occupied countries.

On this point Alexander (1) wrote that, "In view of the known stimulating function of the thyroid gland in the growth of the infant it becomes tempting to relate the hyperactivity of this gland specifically with the apparent need of the hyperthyroid patient to become mature in an accelerated tempo. This constant attempt to master his anxiety and to gain a pseudo-maturity are both very stressful and may serve to activate the secretion of thyrotropic hormone by the anterior pituitary gland which leads to increased thyroid activity."

It should be added here that some investigators refer to environmental influences (Moschowitz) and the importance of an "inherited constitution" in thyrotoxicoses (Brown and Gildea). Wittkower and Mandelbrote emphasize that the etiology of thyrotoxicosis is impossible to explain psychogenetic factors alone. With regard to the specificity of psychic factors they state that similar constellations are found also in tuberculosis, essential hypertension, and rheumatoid arthritis.

From the therapeutic standpoint (2, 3, 25) it must be pointed out that thyrotoxicosis is the only psychosomatic disorder which could be favorably affected by drug therapy and that the somato-psychic aspect of the problem must not be neglected. In addition, thyrotoxicosis is a clinical entity notorious for the spontaneous remissions and exacerbations.

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ON THE RELIABILITY OF CLINICAL EEG INTERPRETATION

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INTRODUCTION

It is universally acknowledged that a test or measurement procedure, clinical or experimental, to be useful must be reliable—that is, that there must be no significant difference in the results regardless of where, when, how, or by whom the operations are performed. In medicine especially, the reliability of a test result must be high to justify drawing conclusions from it which may determine a diagnosis and affect therapy.

In clinical electroencephalography there are several aspects to the problem of reliability. First, there is the reliability of recording instruments. Through cooperation between medical and EEG societies on the one hand and manufacturers of EEG instruments on the other, high reliability of instrumental performance has been achieved. Second, there is the problem of reliability of the recording procedure itself. There is unquestionably more variability among EEG laboratories in recording technique than in instrumentation. EEG societies have also concerned themselves with this problem, and a degree of standardization of technique has been achieved, although standards are less rigidly formalized than in the case of instrument construction and maintenance.

Finally, assuming that a reliable EEG recording has been produced, there remains the question of the reliability of the interpretation of that recording. In the present state of development of electroencephalographic technique and knowledge, clinical interpretation is to a great extent still a subjective procedure. The derivation of clinically useful information depends upon the observational and deductive operations of a more or less well-informed, more or less fallible, human being. The ignorance and fallibility of the electroencephalographer may be the most significant factor in limiting the success of clinical electroencephalographic practice.

It is with this last aspect of the problem of reliability that this paper is concerned. It presents an attempt at experimental evaluation of the reliability of interpretation.[3] For present purposes we mean by interpretation how the electroencephalographer *classifies* the EEG recording, that is, his judgments about whether an EEG is normal or abnormal, if abnormal whether the abnormality is diffuse or focal, if focal the location of the focus, and finally what the nature of the abnormality is (slow waves, spikes, etc.). We deliberately omit from consideration here the electroencephalographer's judgments of the significance of the EEG results in the clinical evaluation of the patient's disorder. This is done to keep the issue simple, to put the emphasis on the reliability problem (does the EEG yield consistent results regardless of where, when, or by whom done?), and for a change to de-emphasize the validity problem (does the EEG correctly answer the question the clinician wants answered?).

The validity problem has been dealt with often. Every paper reporting rates of EEG abnormality and types and locations of ab-

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[3] The only published study of the reliability of clinical EEG interpretation of which we are aware appeared four years ago (Blum, 1954). We shall not report the results in detail since only 10 test records were used—hardly an adequate sample. Suffice to say that five experienced electroencephalographers seemed to come off rather badly in that study.

normal EEG phenomena is essentially a validity study. That clinical electroencephalography is a valid technique in the hands of experienced practitioners has been well-established by numerous such reports over a period of over 20 years. However, the reliability of a test result is a vital factor in determining its overall validity. The less reliable are the test's results, the less valid will the test prove to be.

While we may infer significant reliability from *experimentally established* validity, we cannot determine just how reliable our results are, and we cannot know to what degree the validity of our results may be limited by imperfect reliability. It is desirable to study reliability for its own sake, independently of validity, for if reliability can be improved, validity will consequently also be improved.

We feel that the primary value of a study such as this does not lie in showing such-and-such a percentage of agreement or disagreement of judgments. Limited, as it is of necessity, to a comparison of the efforts of two electroencephalographers, the general applicability of such percentages would be dubious at best. Rather, we feel, its value lies in indicating where the difficulties in interpretation may lie. Thereby it may provide caveats both for the electroencephalographer and for the recipients of his reports.

METHOD

The test records were 140 consecutive EEGs from two laboratories. One of the laboratories (hereafter called "Lab. 1") receives a wide variety of referrals, both neurological and psychiatric cases of both sexes and all ages. The other ("Lab. 2") receives a more limited range of cases, almost entirely adult males, with a larger proportion of routine psychiatric cases than Lab. 1.

The technicians were instructed to make no marks on the recordings other than those necessary to indicate electrode selection and changes in control settings. Most particularly, no marks were to be made indicating possible abnormalities or artifacts.

Two electroencephalographers (EEGrs) interpreted the EEG records independently. One of them is primarily a clinician, a neuropsychiatrist; the other has taught and done research in the EEG field. Both have had over eight years of experience in clinical electroencephalography. The first EEGr (hereafter called "EEGr A") interpreted the records at the time they were recorded and wrote the usual clinical reports. He had access to referral information, and consulted, if he wished, with the technicians about what happened during the recording session. After writing his clinical report he filled out a check sheet, which was coded and kept by the technician.

Several weeks after the last of the test records had been recorded and read by EEGr A, the other EEGr ("EEGr B") read the EEGs and filled out a second check sheet on each. EEGr B read the records "blind"; at the time he made his evaluation he knew only the patient's age and what sedation (if any) had been given. He did not discuss the records with the technicians in order to avoid inadvertent communication between himself and EEGr A through the technicians. After all the check sheets had been completed by both EEGrs, the two sheets for each EEG were compared. The types of disagreements obtained were classified, and then the EEGs on which disagreement had occurred were re-examined.

The Check Sheet. The check sheet was not discussed in detail before the data were gathered. It presented items to be checked under four headings: 1) classification of EEG, 2) degree and distribution of abnormality (if any), 3) focus (if any), and 4) nature of abnormality (if any).

Under *classification of EEG* there were four items: 1) "normal," 2) "abnormal during activation only," 3) "abnormal," and 4) "if 'borderline' classification were permitted, would you so classify this record?"

The choice between normal and abnormal was a forced one, *i.e.*, one and only one of the first 3 items had to be checked. Item 4 could be checked in addition to one of the first 3; this was included to permit an evaluation of the usefulness of the "borderline" category in improving reliability.

Under *degree and distribution* there were four items: 5) "minimal abnormality," 6) "marked abnormality," 7) "diffuse (including bilaterally synchronous)," and 8) "focal." Item 7 or item 8 had to be checked if the EEG had been classified as abnormal. Item 5 or item 6 were checked only if the EEGr thought one or the other adjective appropriate.

Under *focus* there were 21 items (9–29) designating locations of abnormality (if present and if focal).

Under *nature of abnormality* there were six items: 30) "slow waves," 31) "spikes or sharp waves," 32) "spike-and-wave," 33) "fast waves," 34) "asymmetry or asynchrony," and 35) "14 and 6s."

One extra item was provided, permitting the EEGr to designate that the record was clinically useless, if he so judged.

RESULTS

The results of comparing EEGrs A and B on the judgment of normal vs abnormal only are shown in Table 1. The Fourfold Point Correlation (ϕ) computed from Table 1 is .725, standard error .086. χ^2 computed from Table 1 is 71.5086 ($P < .001$).

The overall rate of "abnormal" classifications by EEGr A was 34.8 per cent, that by EEGr B was 35.8 per cent (difference not significant). As Table 1 shows, there was an even split in the "direction" of disagreements: EEGr A called 9 EEGs normal which B called abnormal, and called 8 EEGs abnormal which B called normal; 3 EEGs were called useless by one EEGr but not by the other, and one was called useless by both.

The percentage of agreement for the total sample of 140 EEGs was 85.7. There was no difference between the results obtained in Lab. 1 (85.5 per cent agreement, N = 76) and those in Lab. 2 (85.9 per cent agreement, N = 64). The overall rate of abnormality for the 119 EEGs which were agreed to be either normal or abnormal was 33 per cent. There was a significant difference ($P < 0.02$) between the abnormality rates in Lab. 1 (44 per cent, N = 64) and Lab. 2 (20 per cent, N = 55). This was the only difference between the results obtained in the two laboratories, and the data were therefore pooled.

TABLE 1

Comparison of Two EEGrs on Judgment of Normal vs. Abnormal

	EEGr A		
	Normal	Abnormal	Total
EEGr B			
Abnormal	9	39	48
Normal	80	8	88
Total	89	47	136*

* The 4 EEGs judged to be "useless" by one or both EEGrs are omitted.

Of the 17 EEGs about which EEGrs A and B disagreed on normality, 13 involved possible minimal abnormalities, that is, one EEGr called the EEG minimal diffuse slow (10) or minimal focal slow (3) and the other EEGr called it normal. These records were of several sorts. There were five in which there was a flat disagreement about a waking adult record (Fig. 1A). In one there was a disagreement about the normality of a mild slowing response during hyperventilation; in one about a child's record (Fig. 2); and in two about "focal slowing" during sleep (Fig. 3). Finally, there were four records in which there was apparently no disagreement about the presence of diffuse slow waves, but rather the disagreement appeared to involve the question of whether or not the slowing was due to drowsiness. Here the experimental method was probably a factor, because, as

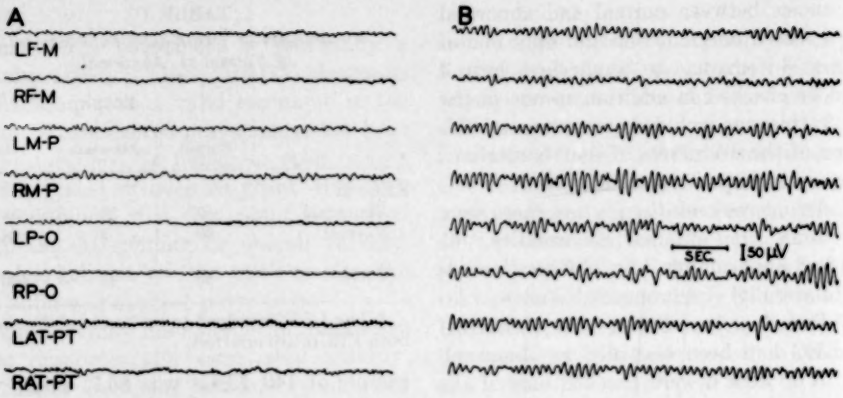

FIG. 1. Disagreements on judgments of normal vs. abnormal. A. Patient aged 24. Reason for referral: "anxiety reaction; headaches." EEGr A classified the record as normal; EEGr B classified it as minimal diffuse slow abnormality. Later in the record a Metrazol activation was done which both EEGrs agreed was negative. B. Patient aged 32. Reason for referral: "head injury; headaches." EEGr A classified the record as normal; B as abnormal diffuse slow.

Labelling of tracings in this and the following figures is according to the following code: L = left, R = right, F = frontal, M = motor (precentral), P = parietal, O = occipital, AT = anterior-temporal, PT = posterior-temporal. See text for further discussion of all figures.

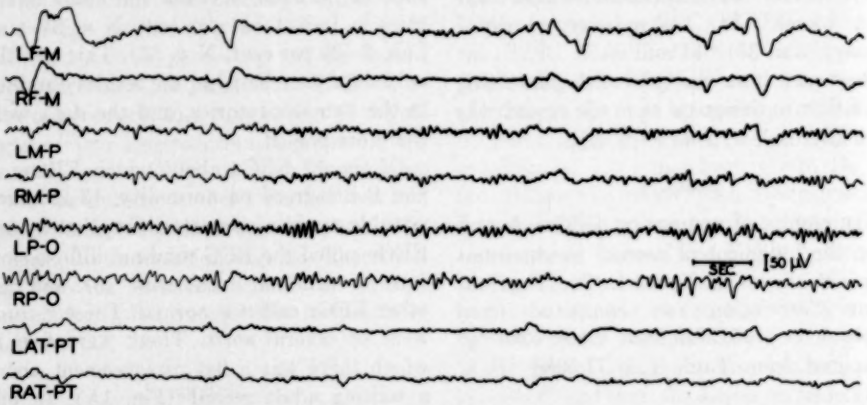

FIG. 2. Disagreement on child's record. Patient aged 12. Reason for referral: "nervous." EEGr A classified the record as normal; EEGr B as minimal focal slow abnormality, bi-occipital.

will be remembered, EEGr B did not communicate with the technicians, whereas EEGr A did. This experimentally necessary restriction of EEGr B may have been responsible for some of these four disagreements and may thus have spuriously lowered the agreement rate.

It was anticipated that disagreements would arise regarding borderline records, and so the item about possible borderline classification was included in the check list to see if the addition of this category might improve the agreement rate. It did not. In fact, when the borderline category was used, the rate of agreement dropped slightly, but insignificantly.

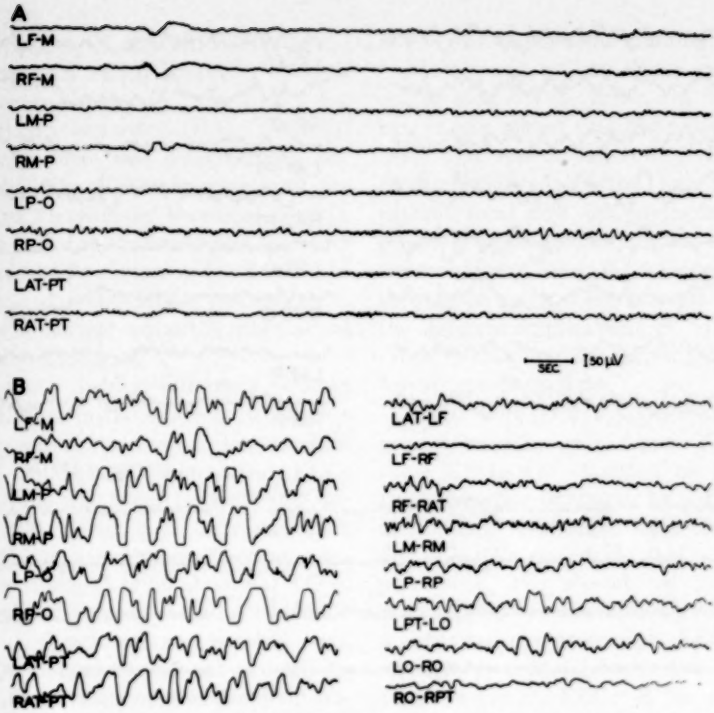

FIG. 3. Disagreement concerning focal slow activity during sleep. A. Patient aged 33. Reason for referral: "headaches, post-traumatic." Light sleep. EEGr A classified the record as minimal focal slow, right parietal-occipital; EEGr B as normal. B. Patient aged two. Reason for referral: "infection, vomiting." Deep sleep. EEGr A classified the record as minimal focal slow, left occipital; EEGr B as normal for age.

In addition to the 13 disagreements just described there were four of a more serious nature. In two cases one EEGr called the EEG abnormal diffuse slow, while the other called it normal (Fig. 1B). In neither of these was the slow activity very marked, and in one of them it was again a question of whether or not the patient was drowsy.

In the other two cases, one EEGr called the records "abnormal focal spikes," and the other called them normal. One of these was a sleep record of a two year old (Fig. 4A); the EEGr who called the record normal, decided on re-examination that he had flatly missed seeing the spikes against the irregular background. The second case was that of a 31 year old (Fig. 4B); the focal "spiking" in this record is admittedly questionable.

Three further disagreements involved the question of whether or not an EEG was useless. There was no disagreement about the fact that these three EEGs were of technically poor quality and should be repeated. The disagreement seemed simply to involve whether any useful information could be gleaned from the records or whether they were absolutely useless. We feel accordingly that a check item "EEG should be repeated" should have been included on the check list. It is clear from re-examination of the records that there would have been agreement on this point on several of the EEGs on which there was

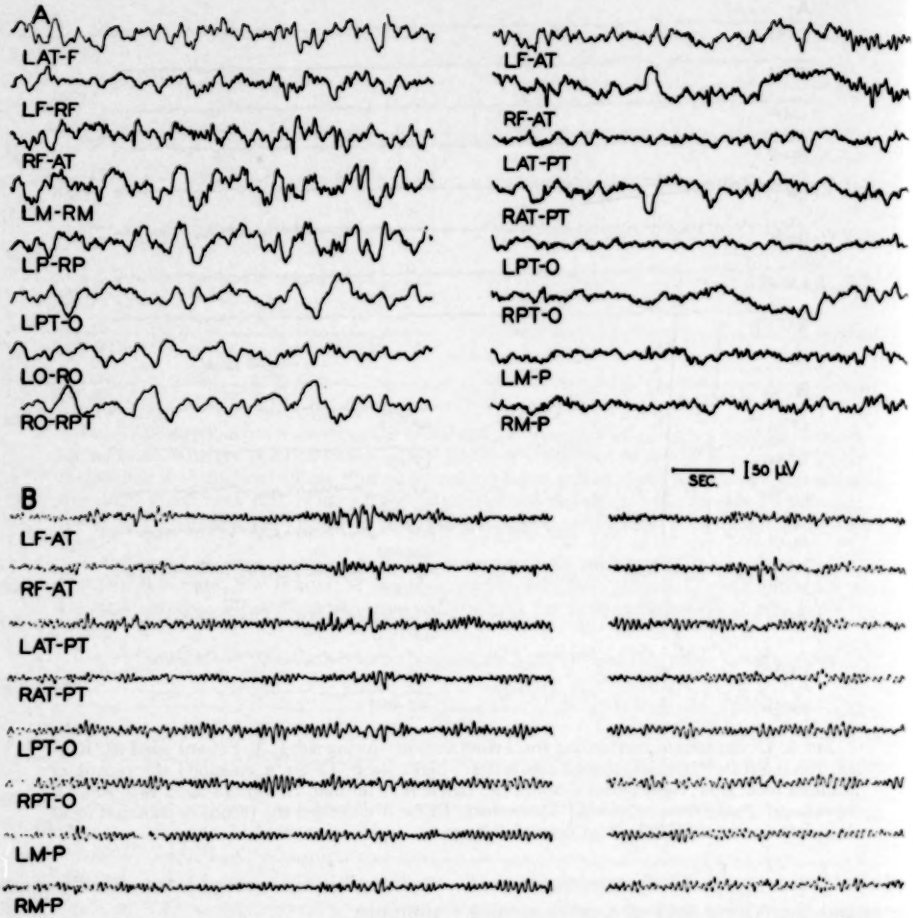

FIG. 4. Disagreement on focal spikes. A. Patient aged two. Reason for referral: "one convulsion yesterday." Asleep. EEGr A classified the record as normal; EEGr B as abnormal focal spikes, right anterior-temporal. On re-examination EEGr A agreed with EEGr B. B. Patient aged 31. Reason for referral: "schizophrenia, paranoid." Awake. EEGr A classified the record as normal; EEGr B as abnormal focal spikes, alternating bi-temporal.

otherwise disagreement on technical quality or on equivocal irregularities in the tracings.

Thirty-nine EEGs were agreed to be abnormal by both EEGrs. Of these there was complete agreement, not only on abnormality, but also on type and location of abnormality in 14 cases. There was some disagreement in 25 cases, but most of these disagreements were of a minor nature.[4]

There was disagreement in 21 of the 39 cases on the degree of abnormality. In other words there was more disagreement than agreement on whether to call a record minimally abnormal, markedly abnormal, or abnormal without a modifying adjective. In 12 of these cases this was the only disagreement, and was considered to be of mi-

[4] Disagreements are considered for present purposes to be *minor* if they are not likely to affect considerations of diagnosis or therapy, to be *major* if they are likely to do so. This classification depends again upon the judgment of those making the decisions, and there may not be general agreement on what may or may not affect diagnosis or therapy.

nor importance. Of the 18 EEGs agreed upon, three were called abnormal by both EEGrs, seven minimally abnormal, and eight markedly abnormal. Of the 21 EEGs about which there was disagreement, one EEGr called the EEG abnormal and the other called it minimally abnormal in seven cases, one called it abnormal and the other called it markedly abnormal in 14 cases. In no instance did one EEGr call a record minimally abnormal while the other called it markedly abnormal.

There was a distinct difference between the two EEGrs in the tendency to use the modifying adjectives *minimal* and *marked*. Of the 21 instances of disagreement, EEGr A was the one who used the modifying adjective in 20, EEGr B in only one case. Overall, EEGr A used the adjective *minimal* in describing 13 of 39 abnormal EEGs, and the adjective *marked* in describing 22. EEGr B used *minimal* and *marked* eight times each. It is clear that the two EEGrs conceptually divided up the degree-of-abnormality continuum differently. The middle part of the distribution, called abnormal (unmodified), was narrower for EEGr A than for B; B tended to apply modifying adjectives only to more extreme cases.

If one considers the continuum *normal-minimally abnormal - abnormal - markedly abnormal* as a 4-step scale, it is found that there was agreement on scale position in 95 of 136 EEGs (omitting the four "useless" ones). There was disagreement of one step in 39, and of two steps in two cases. There were no disagreements of three steps.

There was one disagreement on type of abnormality only. EEGr A called the EEG of a 33 year old mixed fast and slow, B called it slow only. There was no doubt that the slow component was the most prominent. We considered this a minor disagreement.

There were two disagreements on locus of abnormality only, that is, EEGs which one EEGr considered to be diffusely abnormal and the other focal. Both involved slow wave abnormalities. The first of these EEGs was classified as minimal focal slow, right occipital, by one EEGr and minimal diffuse slow by the other. On re-examination it was agreed that the record was diffuse. The second EEG was classified as marked diffuse slow by one EEGr and marked focal slow, left hemisphere, by the other. On re-examination it was agreed that the record was focal. We considered both of these to be major disagreements, because of the different implications of "diffuse" and "focal", although the abnormality in the former case was slight.

There were two disagreements on the precise location of a focus. The first of these EEGs was classified as focal slow, right posterior-temporal by EEGr A and as minimal focal slow, right temporal, by EEGr B. We considered this a minor disagreement. The second we considered a major disagreement although the abnormality was not prominent. EEGr A classified it as minimal focal slow, right posterior-temporal, EEGr B as focal slow, bioccipital.

There were five disagreements involving both type and locus of abnormality and two involving both type and precise focus of abnormality. Five of the seven were considered major disagreements:

1. Patient 43 years old. EEGr A classified the EEG as minimal focal spikes, left temporal; EEGr B as minimal diffuse slow. The spikes were of the "small sharp" type of Gibbs (Fig. 5A). On re-examination EEGr B considered them probably significant.

2. Patient seven years old. EEGr A classified the EEG as marked diffuse spike-and-wave with focal tendency, left frontal; EEGr B as marked focal spikes and spike-and-wave, multiple foci. Although these classifications do not seem to differ greatly, we listed the disagreement as major.

3. Patient 15 years old. EEGr A classified the EEG as marked focal spike-and-wave, left precentral; EEGr B as diffuse spikes and spike-and-wave. On re-examination EEGr B agreed that there was a focal tend-

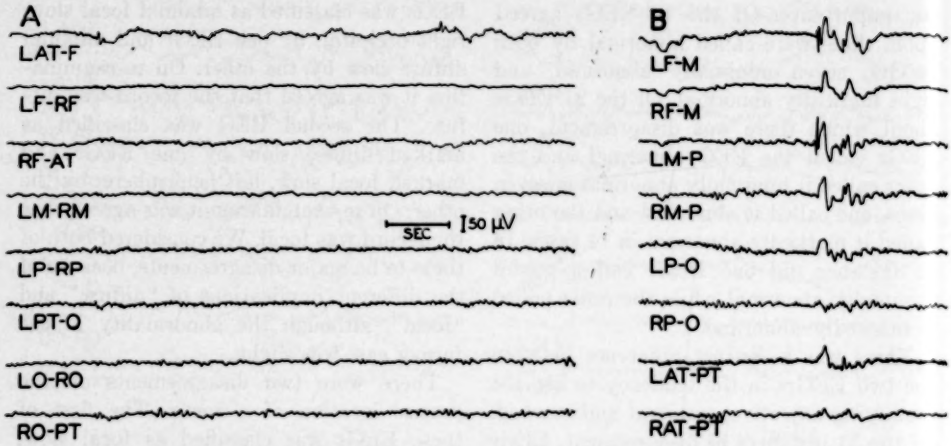

FIG. 5. Disagreements on location and type of abnormality. A. Patient aged 43. Reason for referral: "one convulsion two days ago." EEGr A classified the record as minimal focal spike abnormality, left temporal; EEGr B as minimal diffuse slow abnormality. B. Patient aged 15. Reason for referral: "three convulsions three weeks ago." EEGr A classified the record as marked focal spike-and-wave abnormality, left precentral; EEGr B as diffuse spike and spike-and-wave. EEGr B on re-examination agreed with EEGr A with regard to the focal tendency.

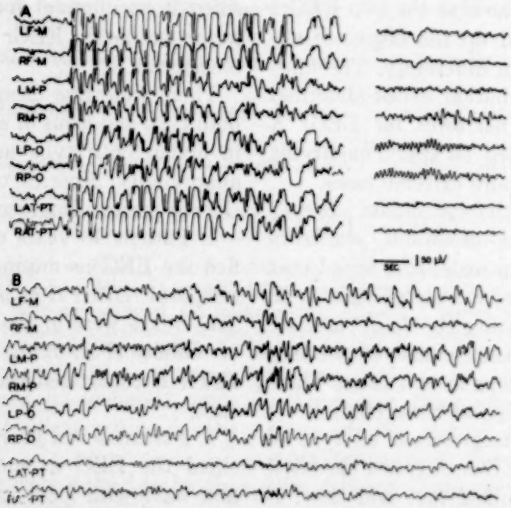

FIG. 6. Disagreements on location and type of abnormality (continued). A. Patient aged eight. Reason for referral: "question of petit mal." Asleep in strip on left; awake in strip on right. EEGr A classified the record as marked diffuse spike-and-wave abnormality; EEGr B as marked diffuse slow and spike-and-wave and focal spikes, right parietal. B. Patient aged 11. Reason for referral: "convulsions; auditory sensations (aura?); 'foggy' sensation." Asleep. EEGr A classified the record as marked diffuse spike-and-wave and focal spikes, left and right precentral; EEGr B as abnormal diffuse spikes and spike-and-wave. The diffuse spike-and-wave discharges appeared in another section of the record while the boy was awake, and there was no disagreement about them; the strip illustrated shows the section of sleep record on which EEGr A based the second part of his classification, "focal spikes, left and right precentral."

ency, the spike-and-wave complexes being of greater amplitude on the left side, especially in the left precentral area, most of the time (Fig. 5B).

4. Patient eight years old. EEGr A classified the EEG as marked diffuse spike-and-wave; EEGr B as diffuse slow and spike-and-wave and focal sharp waves, left parietal. The diffuse spike-and-wave discharges were the most striking feature of this record (Fig. 6A); the focal spikes were seen only transiently.

5. Patient eleven years old. EEGr A classified the EEG as marked diffuse spike-and-wave and focal spikes, left and right precentral; EEGr B as abnormal diffuse spikes and spike-and-wave. The disagreement involved the second part of EEGr A's classification. On re-examination of the EEG the section of sleep recording giving rise to the disagreement was found (Fig. 6B). EEGr A judged the sharp waves shown to be spikes; EEGr B judged them to be sleep "humps." Neither EEGr is now sure which, if either, is correct, and there has been considerable disagreement among other EEGrs who have inspected this record.

6. Patient 35 years old. EEGr A classified the EEG as minimal focal sharp waves, right temporal; on his clinical report he had written, "Possible right temporal abnormality. Conclusiveness of abnormality remains in doubt." EEGr B classified the EEG as minimal diffuse slow.

7. Patient ten years old. EEGr A classified the EEG as marked focal spikes, right precentral, and diffuse slow; B as focal spikes right temporal-central, especially central. B did observe the diffuse slowing, but considered it too minor to be included. The differences between these two classifications would seem to be merely a matter of emphasis, and we considered them to be of minor importance.

Overall, there was agreement on locus of abnormality (diffuse vs focal) in 31 of 39 abnormal EEGs (20 diffuse, 10 focal, one diffuse+focal). There was agreement on precise focus in seven of eleven focally abnormal EEGs, the differences in two others were minor, and in one, while the difference in localization was significant, the abnormality was judged to be minimal by both EEGrs. In no case was there a disagreement involving a lateral or quadrantic shift. Type of abnormality was agreed upon in 31 of 39 EEGs. All but one of the eight disagreements were instances in which one EEGr checked more than one type of abnormality, while the other checked only the most prominent type of abnormality (usually *spikes and spike-and-wave* vs. *spike-and-wave* only).

TABLE 2

Summary Table: Comparison of Two EEGrs Interpreting 140 EEGs

	N		%
A. Complete Agreement			
1. Normal	80		
2. Abnormal	15		
3. Useless	1		
Subtotal		96	68.6
B. Minor Disagreement			
1. Normal vs. min. abnormal	13		
2. Degree of abty. only	12		
3. Useless	3		
4. Location and/or type of abnormality	4		
Subtotal		32	22.9
C. Major Disagreement			
1. Normal vs. abnormal	4		
2. Location and/or type of abnormality	8		
Subtotal		12	8.5
Grand Total		140	100.0

Table 2 provides a condensed summary of these results. The disagreements have been divided in the table, on the basis of the criteria cited above, into those of major and minor importance. This division is of necessity and admittedly arbitrary. Others may not agree with some of these judgments, but disagreements (and errors) do vary in clinical importance, and we felt that an attempt should be made to classify them on that basis.

DISCUSSION

It is evident that our rate of agreement cannot be accounted for on the basis of the operation of chance factors alone. While there were disagreements on 31 per cent of the 140 test EEGs, most of them were of a minor nature. On the other hand, since we did find 8.5 per cent major disagreements, good cases can be made for obtaining second opinions on clinical EEGs when in doubt, and for obtaining two or more independent interpretations of EEGs used as research data. We trust that it is needless to point out the value of obtaining repeat EEGs in doubtful cases. The qualified EEGr will do so whenever in doubt to verify his first results, and so will increase his reliability.

It should be noted that imperfect reliability does not call the results of validity studies into question. Electroencephalography is a valid and valuable technique in the evaluation of many brain disorders. That the method is not perfectly reliable (and no clinical test procedure is), does not detract from this fact. Moreover, the reliability of EEG interpretation is apparently good. The point is that it could be better, and to the extent that it may be improved, validity may likewise be improved.

It should further be re-emphasized at this point that these results should not be taken as necessarily representative of the performances of EEGrs in general. We do not know whether these results are typical or not. To the extent to which the restrictions and imperfections of the experimental design contributed to disagreements, our rates of agreement are undoubtedly spuriously low. We feel that the principal value of this investigation is in indicating the possible sources of unreliability. We will discuss these under four headings: 1) experimental method, 2) ambiguity of tracings, 3) errors of judgment, and 4) semantic factors.

Experimental method. As we have previously indicated, certain aspects of the experimental procedure may have to some degree contributed to unreliability. These are: 1) lack of discussion of the check list items before the beginning of the study, 2) differences between EEGrs A and B with regard to access to correlative data, and 3) the forced-choice, discrete-category nature of the check list.

It is well-known that thorough discussion of a check list's items by its users tends to increase its reliability. Such a discussion was omitted because we were studying reliability for its own sake, and wanted each EEGr to employ his own workaday concepts. Since the two EEGrs were already familiar with each other's methods and concepts, it is not felt that omission of discussion of the check list items had a significant effect on reliability in this study, except perhaps with respect to the use of the adjectives *minimal* and *marked*. A colleague has pointed out that failure to make explicit the method of checking multiple abnormalities may also have had an adverse effect.

The fact that EEGr A had access to collateral information, including both referral data and information obtained from the technicians concerning occurrences during the recording session, while EEGr B read the records "blind," probably did affect the results. Half-a-dozen disagreements, including one major disagreement, may be attributable to this factor. As we have indicated, the reason for this procedure was to prevent even inadvertent communication between EEGr A and EEGr B through the technicians, which we still consider important. However, we feel that this is a defect in our procedure, which should be corrected in similar future studies, perferably by having both EEGrs read the records "blind," at least initially.

Forcing the judges to make choices between discrete categories on a check list without opportunity for qualification, may result in differences in judgment which are more apparent than real. Our data show that this can happen, especially on EEGs in

which the presence or nature of the abnormality is ambiguous. In several cases where there was disagreement on forced choice items, examination of EEGr A's written report showed that he had some reservations about the way in which he cast his vote. We have no way of knowing how often this occurred with EEGr B, except in one case where he added a note to his check sheet.

On the other hand, the use of a forced-choice discrete-category check list is highly desirable in this kind of a study, because it forces the judges to commit themselves on the difficult as well as on the easy cases, and it makes their judgments strictly comparable. Further, as our data seem to show, the use of qualifying phrases or adjectives, as well as of a "waste-basket" category for ambiguous records (*i.e.*, "borderline"), may actually decrease, rather than increase, reliability. The borderline category did not increase the number of our agreements, and the use of the qualifiers *minimal* and *marked* was responsible for 21 disagreements. The greater the number of categories used, the greater the opportunities for disagreement. The greater the variety of words and modes of expression permitted in describing a phenomenon, the greater looms the semantic problem.

A satisfactory compromise in this type of study might be to have both (or all) judges read the EEGs "blind" and fill out a check list, and then give them access to collateral information and have them write a clinical report, so that both kinds of data would be available.

Ambiguity of tracings. Many phenomena seen in EEGs are simply not clear-cut. Every EEGr is all too familiar with the "spike" which is not quite a spike, the spike-and-wave complex which is not quite so. Just how many slow waves of what frequencies must be present to make a record abnormal?

Ambiguity cannot be eliminated entirely, since there is no clear dividing line between normality and abnormality in electroencephalography any more than there is one between health and disease. Ambiguity is an important, probably the most important, source of unreliability in electroencephalography, and promises to remain so as long as interpretation is impressionistic and qualitative.

In our opinion, at least 27 of the 44 disagreements in the present data including four of the 12 major disagreements, can be attributed to ambiguity of tracings themselves (for example, Figs. 1, 2, 3, 4B, 6B), so that even if all other sources of unreliability were eliminated, the rate of agreement would not be much higher than 80 per cent with about three per cent major disagreements. This is not to say that the rates could not be better with other pairs of judges, or with a different check list.

We had expected that the rate of agreement with children's EEGs would be lower than with adults' in view of the generally recognized greater ambiguity of criteria of normality for children's EEGs. This however was not the case with this series. The proportion of disagreements with children's EEGs was no higher than with adults'.

Errors of judgment. Errors of judgment may be of two types, those attributable to ignorance and those attributable to mental lapses. Through ignorance, a phenomenon agreed to be abnormal by authorities on the basis of research may be passed over as normal, or a normal phenomenon may be called abnormal. As far as we have been able to determine, no disagreements in the present data are attributable to this factor. On the other hand, it is unquestionably an important problem, and possibly more so with children's EEGs than with adults'.

Whereas the incidence of errors due to ignorance is doubtless inversely related to quality of training and length of experience, the incidence of mental lapses is very likely unrelated. By "mental lapse" we mean failure to see a phenomenon which is clearly recognized and agreed to be significant when it is pointed out. This kind of

error, which is certainly unfortunate, did occur three times in the present series, accounting for three of the 12 major disagreements.

Semantic factors. Semantic problems are not unrelated to the previous considerations. There is no need to engage in an extensive discussion of the problems of linguistic communication. That different EEGrs may use different words to describe the same phenomena and may attribute different significance to the same words is obvious. Where the recipient of an EEG report is familiar with the usage of the writer, there may be very little failure of communication; where he is not, confusion may be considerable. We suspect, further, although we have no specific data to support the suspicion, that there is often a direct relationship between ambiguity of the EEG phenomena observed and the ambiguity of the resulting report.

The use of a check list largely precludes demonstration of the effects of differences in word usage, but some indications were observed. The most obvious case in point was the difference in the use of words *minimal* and *marked*. Further, examination of EEGr A's clinical reports showed greater use of qualifying phrases and statements in cases where the EEGrs disagreed. "Hedging" in clinical EEG reports may be an indicator of unreliability.

Semantic difficulties are probably less likely to occur in connection with substantives than with modifiers, but they can occur. This is illustrated by four disagreements about the use of the terms *spike* and *spike-and-wave*. Many sporadic spikes are followed by a more or less prominent slow wave. Should the discharge be called a spike or spike-and-wave? When the slow component is of low voltage and variable, one is probably justified in calling it a spike, and when it is of high voltage and regular, a spike-and-wave. But what of the intermediate form? Again it is apparent that the semantic problem is not unrelated to that of ambiguity of tracings. If we had separated *spikes* from *sharp waves* and *spike-and-wave* complexes from *sharp-and-slow* complexes on the check list (as there in fact seem to be good clinical reasons for doing), we would probably have obtained a few more disagreements than we did.

How may reliability be improved? We would suggest by: 1) standardization of training, 2) standardization of nomenclature, and 3) quantification and objectification of interpretive techniques. If EEG training, nomenclature, and laboratory procedures were as well standardized as recording equipment, we would have progressed a long way toward completely reliable clinical electroencephalography.

In his comment on Blum's paper, Aird states, "Comparison of interpretations of a given number of electroencephalographic records by a series of electroencephalographers . . . is a test of the relative homogeneity of the background and training of the electroencephalographers concerned, and this latter is known to vary considerably." It is well for the physician who refers patients for EEGs to bear this in mind, and above all to *know his electroencephalographer.*

Electroencephalography is a relatively new field and its subject matter is complex. It is to be hoped that by further standardization and objectification of its procedures even more reliable results than are now possible can be attained.

On the other hand, we would not want to go so far in standardization as to suppress individuality. The proper balance between standardized methods and nomenclature (which tend to improve reliability and accuracy of communication) on the one hand and the free play of individual imagination (which is the source of progress) on the other, is a perennial and ubiquitous problem in science. There is no pat formula for its solution. We would suggest, however,

that perhaps individuality is more appropriate in the research than in the clinical laboratory. Certainly general adherence to a standardized nomenclature would improve reliability and communicability. Although attempts have been made along this line, in practice there is far from anything approaching universal usage.

The several EEG societies have encouraged standardization of training, but in view of the wide variety of auspices under which EEGrs are trained, the problems are many and not easily solved. Progress will only be made as adequate numbers of EEGrs are trained by those present leaders in the field best qualified to teach them. But again an extreme position is to be avoided. No one, we hope, would recommend doctrinal training programs, even for clinical EEGrs who intend to do little or no research.

Objectification and quantification of interpretive operations are also goals to be sought. Automatic frequency analysis and the more recent autocorrelation and cross-correlation techniques are examples of the sorts of things that can be done in this direction. These instruments certainly do not replace the clinical EEGr, nor were they meant to, but in certain instances they may assist him. Further developments in instrumentation are bound to come.

In the meantime, it would be interesting if additional pairs or groups of EEGrs would compare their clinical interpretations, one with the other, or if individual EEGrs would test their own reliability by the test-retest method, rereading EEGs after a lapse of time. As we have repeatedly stated, the present data are inadequate to estimate the general reliability of EEG interpretation. Others may do better.

SUMMARY

Two EEGrs independently evaluated 140 consecutive clinical EEGs. Disagreements were classified and presented.

The sources of unreliability of EEG interpretations (other than those inherent in the experimental design) revealed by this study are:

1. *Ambiguity of the tracings.* This is the most important source of unreliability, accounting for over two thirds of the disagreements. The use of a specific category meant to cover some ambiguous records (*i.e.*, "borderline") did not increase the number of agreements. There was not any apparent difference in the present series between adults' and children's EEGs with respect to ambiguity leading to differences in interpretation.

2. *Errors in interpreter judgment* accounted for three disagreements.

3. *Semantic factors*, that is, differences concerning what terms to apply to observed EEG phenomena, seemed to account for most of the remaining disagreements, but since ambiguity of word usage is closely related to ambiguity of the phenomena observed, definite proportional responsibility cannot be allotted to these factors separately. A positive relationship between ambiguity of the verbal EEG report and unreliability of interpretation is suggested.

Suggestions were made for improving the experimental design. Suggestions were also made concerning ways of increasing the general reliability of EEG interpretation, realizing that the problems are complex and not easily solvable.

REFERENCE

1. Blum, R. H. A note on the reliability of electroencephalographic judgments. Neurology. **4**: 143–146, 1954.

The following paper is published in the interest of acquainting Western clinicians and investigators with some of the work and thinking currently in progress in the USSR. It is hoped that this article will have special value and interest despite the difficulty of checking certain references and of establishing ready communication with the author.

The Editors

FUNCTIONAL STATE OF HIGHER SEGMENTS OF THE CENTRAL NERVOUS SYSTEM AND ADRENOPITUITARY ACTIVITY[1]

V. TRACHIK

In the past twenty years rather significant achievements have been made in the study of the chemical and physiological properties of the hormones of the adrenal cortex and of the anterior lobe of the pituitary. The well-known Canadian scientist, Hans Selye, in papers published in the 1930's brought attention to the anterior pituitary and the adrenal cortex in connection with reactions of the organism in acute stress.

Selye's observations on the reactions of the organism to pathogenic agents were based, at first, on morphologic studies. In later investigations he studied the influence of various kinds of traumatic effects on the organism of animals who received adrenal cortical hormones in addition.

Generalizing from his own investigations and from the observations of other authors, Selye advanced the theory of the general adaptation syndrome in 1946. This theory postulates that the anterior pituitary and the adrenal cortex are responsible for the reaction of the organism to acute stress.

In a monograph (30) in 1946 as well as in a book published in 1950 (31) Selye examines the possible stimulators of the general adaptation syndrome, and lists nervous stimulation among others. He believes that in the development of the so-called anxiety reaction, which is the first of the three phases of the general adaptation syndrome, nervous impulses may play an important role.

In explaining the mechanisms of reaction of the organism to acute stress, Selye does not mention the nervous regulation of functions in the organism, despite his earlier statements in favor of such a reaction. He points to the hypothalamic region, which, influenced partially by the afferent nervous stimulation from the injured area and partially by humoral substances, may aid in the development of the general adaptation syndrome.

In other sections of his work Selye directly states that the path through which the pathogenic irritant (stressor) stimulates the hypothalamic area and the pituitary is unknown. Moreover, in certain of his works Selye attempts to prove by experimental means that the response of the organism to injury is due only to humoral regulation. As an example he cites his work with Fortier (6) on transplantation of the pituitary into the anterior chamber of the eye.

One can reach only one conclusion from the totality of Selye's statements, namely, that the theory of the general adaptation syndrome pertains to the humoral theory of the regulation of functions of the organism. Exclusion of the central nervous system and its higher segments from the reaction of the organism to acute stress is, in our opinion, a grave shortcoming of Selye's position. It is necessary to suppose that the stimulus first reaches the central nervous system and its higher divisions, and only then does the functional state arising in them decide the fate of the reaction of the pituitary-adrenal system.

[1] TRACHIK, V. Prob. endokrinol. i gormonoterak., **3**: 25–34. 1957. Translation of this paper has been furnished by the National Institutes of Health, Public Health Service, as a part of their Russian Scientific Translation Program.

The solution of this problem is a rather difficult task, in view of the contrary opinions existing in the literature regarding even the determination of the paths through which the regulation of the secretion of the anterior pituitary and the adrenal cortex is accomplished.

A number of authors do not accept the theory of direct nervous regulation by the anterior pituitary—Fortier and Selye, Cheng *et al.* (4); others believe that nervous regulation is accomplished indirectly through the medullary substance of the adrenal gland, and that adrenalin increases the secretion of ACTH (22, 38). Certain authors take the position that the sympathetic nerves reaching the pituitary from the cervical sympathetic plexus, are the nerves which regulate anterior pituitary functions (17, 34, 35, 37).

The presence of secretory innervation of the adrenal cortex has not yet been established either by morphologic means (13, 14) or by physiologic methods (38, 39, 40).

There are experimental observations in the literature indicating an influence of the removal of the adrenals or of the hypophysis on the functional state of the higher divisions of the central nervous system, as determined by the objective conditioned reflex method. This is the work of M. N. Yurman (41), V. Ya. Kryazhev (15), and D. M. Gzgzyan (8, 9).

The literature, however, yields very few observations indicating an influence of the higher branches of the central nervous system on adrenal-pituitary activity. One can only mention the reports of Pincus (23, 26), Pincus and Hoagland (24), and Pincus and Elmadijan (25). Pincus and his associates observed increased excretion of 17-ketosteroids in their subjects during severe mental and emotional stress. Pincus (23) noted that the amount of 17-ketosteroids in the urine indicates the degree of adrenocortical activity, and is positively related to the degree of psychic exhaustion that is manifested.

The experiments of S. P. Nikolaychuk (18) also indicate a link between pituitary-adrenal activity and the higher divisions of the nervous system. Using dogs with cotton tampons placed on areas 6 and 17 of the cerebral cortex, Nikolaychuk observed a reduction in the content of 17-ketosteroids in the adrenal cortex on the thirteenth and even the thirtieth day after operation. This would support the theory that elevation of the secretion of the pituitary-adrenal system is prolonged after the placing of tampons on the cerebral cortex.

The above observations indicate only a link of the pituitary-adrenal activity with the cortex of the brain; however, the initiating and correcting role of cortical signals, as formulated by K. M. Bykov (2), in the basic regulation of the pituitary-adrenal system, has remained unstudied up to the present time.

In this connection, we have attempted experimentally to determine whether definite functional states of the higher divisions of the central nervous system in highly organized animals (dogs) exercise an influence on pituitary-adrenal activity.

METHOD

Experiments were run on three female dogs with ureters diverted to the skin by the technique originated by Pavlov in 1883 and modified by I. S. Tsitovich (36) and L. A. Orbeli (19), and with a fistula of the parotid gland. The dogs were kept on a strictly controlled regimen of feeding and care.

In order to study the higher nervous activity of the experimental animals, a system of positive and negative auditory and visual conditioned reflexes was established. The dynamic stereotype of the conditioned stimuli consisted, in the first and third dogs, of six positive and four differentiating—negative—conditioned stimuli. In the second animal six positive and two differentiating stimuli were used. This particular animal could not tolerate more than two differentiating stimuli in an experimental day.

As positive conditioned stimuli we used the sound of a bell, and a flickering lamp of 100 watts, and 120 beats of a metronome per minute. The negative differentiating stimulus, to the positive metronome of 120 beats per minute, was 60 beats of the metronome per minute.

In the first two animals reinforcement of the positive conditioned reflex was food (sugar), and in the third dog the reinforcement was a solution of hydrochloric acid.

After reinforcement of both the positive and the negative conditioned reflexes, tests were run on the animals to determine the type of their nervous systems. These tests were conducted, basically, according to minimum specifications of the determination of the type of the nervous system (27). Certain modifications were necessary, since our opportunities were limited by the conditions of the method, primarily by urine collection during the experiment.

The type of nervous system was established in order to determine whether there was a relationship between the typological peculiarities of our experimental dogs and the urinary excretion curve of 17-ketosteroids. In addition to the determination of the type of nervous system, our task was to provoke a chronic pathological state of the cells of the cerebral cortex. This was achieved by inducing chronic overstress of the mobility of the nervous processes at time of revision (in the first and second dogs) and by a chronic overstress of the strength of the inhibitory process (in all three dogs). The chronic overstrain of the strength of the inhibitory process in the experimental animals was induced by the use, over the course of several days in succession, of the differentiating stimulus prolonged from twenty seconds to ten minutes and simultaneously intensified in its physical strength. The intensification was achieved by transmitting the strokes of the differentiating metronome through a microphone and an amplifier at a power level of ten watts.

Experiments on the animals were always begun with the administration of 250 ml. of a water-milk mixture. Urine flowing from the ureters was collected and measured at ten-minute intervals over the three hours of the experiment. Thus the course of diuresis could be studied, as well as the total amount of urine excreted in three hours.

The activity of the pituitary-adrenal system was studied by means of determining the neutral 17-ketosteroids in the urine. The neutral 17-ketosteroids in the urine were determined with the aid of a method described in 1938 by N. Callow and R. Callow (3), as modified by Seeman and Azerad in 1950 (29), with the use of a color reaction suggested in 1935 and 1936 by Zimmerman (42, 43).

Studies of 17-ketosteroids in the urine of laboratory animals in general, and in dogs in particular, are far fewer than clinical studies. The literature, however, does report studies of the 17-ketosteroids in the urine of dogs under acute stress. Heusghem and Charlier (10) observed an elevation of the excretion of the 17-ketosteroids in the urine in dogs poisoned with mustard gas, and Lawrence (16) noted a significant elevation of the excretion of 17-ketosteroids in connection with roentgen irradiation. N. A. Isichenko and Ye. Z. Gincherman (11, 12), studying experimental hypertension elicited by suturing the adrenal cortex of dogs, also noted an elevated daily content of 17-ketosteroids in the urine.

In addition to these reports which indicate the suitability of determining 17-ketosteroids in the study of the function of the adrenal cortex in dogs, there also exist observations negating this. Bekaert and Demeester (1), Duffy (5) and Glenn and Heftmann (7) did not observe a noticeable increase in the daily content of 17-ketosteroids in the urine of dogs, after injection of ACTH. These investigators concluded

that, in contradiction to observations made in man, the urinary 17-ketosteroids in dogs do not reflect the function of the adrenals.

It should be especially noted that these latter writers noted a lower 17-ketosteroid content in the daily urine of dogs than did the writers mentioned earlier. This might suggest that during the time of determination there occurred a significant disintegration of the 17-ketosteroids, which could account for the lowered levels reported. Tewell and Freeman (33) have repeated the experiments of the authors who deny the usefulness of the determination of 17-ketosteroids in dogs, and have obtained contrasting results. These investigators observed an elevation of the content of 17-ketosteroids in the daily urine of dogs, following the intravenous injection of ACTH.

In view of the disagreements in the literature, we also subjected this question to test. Following the intravenous injection of five mg. ACTH per kg. body weight of the dog, we observed a significant rise in the content of 17-ketosteroids in the urine collected over the period of three hours after the injection. The rise in the content of 17-ketosteroids in the urine following the injection of ACTH was observed in every instance in which a low excretion had been noted in preliminary (control) experiments; the intravenous injection of ACTH on a background of already elevated excretion of 17-ketosteroids was not accompanied by any further elevation.

Hence, on the basis of the findings in the literature and our own experiments we believe that the content of 17-ketosteroids in the urine of dogs, as well as in man, does reflect pituitary-adrenal activity.

In addition to studying 17-ketosteroids, we also studied renal filtration and reabsorption for the three hours of the experiment, according to a method worked out for dogs in 1928 by L. A. Orbeli, Ye. A. Asratyan, A. A. Danilov, and A. A. Mikhel'son (20). For this purpise we determined the endogenous creatinine in the blood plasma by a method described by Popper, Mandel, and Mayer (28), and the creatinine excreted in the urine.

To avoid errors arising from variations in the renal filtration, we employed, in the evaluation of our results, not only the absolute amount of 17-ketosteroids excreted during the experiment, but also the coefficient: Coefficient equals the absolute amount of 17-ketosteroids excreted during the three hours of the experiment divided by the absolute amount of creatinine excreted during the three hours of the experiment.

On the basis of the amount of 17-ketosteroids excreted in the urine in the course of the experiment and on the basis of the coefficient, we were able to detect the rise or fall of the function of the adrenal cortex and also its stimulation by ACTH of the anterior pituitary.

The investigations of the conditions of the experiment were always rigorously identical; only the conditioned stimuli, their signal meaning, prolongation and strength were changed. Hence changes in the amount of 17-ketosteroids excreted in the urine should reflect the state of the higher nervous activity of the experimental animals, and not other factors.

RESULTS

In the first dog, weighing 11.5 kg. and about five years of age, 293 documented experiments were run over the course of more than two years. Creatinine was determined in the urine collected during 280 experiments, and 17-ketosteroids in the urine collected in 275 experiments.

In the second dog, weighing 18.6 kg. and about eight years of age, 190 documented experiments were run over the course of 14 months; creatinine and 17-ketosteroids were determined in the urine collected in 176 experiments.

In the third, a young dog weighing 16.5 kg., 99 documented experiments were run over the course of a single year. The creatinine was determined in the urine collected in 88 experiments, and 17-ketosteroids in the urine collected in 85 experiments.

On the basis both of applied tests and of the general progress of the work on the conditioned reflexes, the nervous system of the experimental animals could be characterized as follows. The first dog was *strong, balanced, passive*; the second was of intermediate type, between *strong, balanced, lively* and *weak*; and the third dog was *strong, unbalanced*, and *lively*. The amount of 17-ketosteroids in the urine for the three hours of the experiments averaged 181.4 gamma, 296.7 gamma, and 319.7 gamma respectively.

Observing the cortical dynamic, we were able to demonstrate a connection between the functional state of the higher divisions of the central nervous system and the variations in the amount of the 17-ketosteroids excreted in the urine. In the periods of application of the usual stereotype, with an established balance between the processes of stimulation and the processes of inhibition, a low content of 17-ketosteroids was observed in the urine of the three dogs. The variation of content of 17-ketosteroids in the urine did not go beyond the limits of 100 to 300 gamma. In the periods of disruption of the balance between the processes of stimulation and of inhibition, there was observed an elevation of the excretion of 17–ketosteroids in the urine.

The first experiments run on the second animal in the period of establishment of a dynamic stereotype, could serve as an example of a sharp disturbance of balance. The introduction in experiment No. 29 (March 27, 1954) of the third differentiating stimulus (M-60) deepened a hypnotic state noted earlier (Figure 1). The most profound hypnotic state was noted in experiment No. 31. The conditioned reflex declined to almost zero; moreover, the first

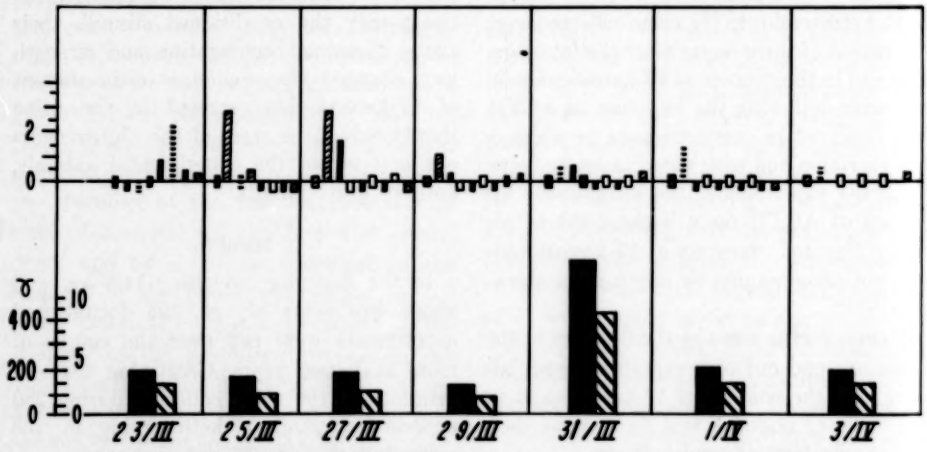

FIG. 1. Second dog. Upper columns show the magnitude of the salivary conditioned reflexes in drops of saliva. Each division represents ½ drop of saliva. Above the abscissa—the magnitude of the conditioned reflexes during the time of the isolated action of the stimulus; on the abscissa—the brief conditioned stimuli; under the abscissa—conditioned stimuli; under the abscissa—conditioned stimuli not accompanied by salivation.

Columns with cross stripes—conditioned reflexes to M-120; columns with diagonal stripes—conditioned reflexes to the buzzer; white columns—conditioned reflexes to the flickering light; black columns—conditioned reflexes to the differentiating stimulus M-60.

Lower columns in black—17-ketosteroids in gamma; striped columns—coefficient for the three hours of the experiment.

manifestations of a prolonged latent period, reaching ten to twelve seconds for the unconditioned stimulus (food) were noted in this dog.

In the urine collected during this experiment the content of 17-ketosteroids attained to 665 gamma, which, even in comparison with the preliminary experiments, is an elevation of content of 17-ketosteroids in the urine to 235 per cent and of the coefficient to 471 per cent.

Overstrain of the strength of the stimulatory process in the cells of the cerebral cortex arising in the course of determining the type of nervous system, was accompanied in our three dogs by an insignificant elevation of either the content of 17-ketosteroid in the urine or the magnitude of the coefficient.

The two-phased revision of the signal meaning of the conditioned stimuli could not be accomplished with either the first or the second dog, despite 40 trials. There were observed simultaneously, in the first and the second dogs, disturbances of the higher nervous activity. On the basis of this it was necessary to regard the experiments during the period of revision as chronic overstrain of the mobility of the nervous processes. In these same experiments the content of 17-ketosteroids in the urine averaged higher: in the first dog, to 32 per cent (the coefficient to 47 per cent); in the second dog, to 20 per cent (the coefficient to 60 per cent) in comparison with earlier control experiments run under conditions of normal and characteristic higher nervous activity for experimental dogs.

To illustrate, let us refer to experiments with revision, run on the second dog. In Figure 2 is shown the curve of higher nervous activity and of the excretion of 17-ketosteroids in the urine.

In experiments from No. 117 to No. 136, the positive conditioned stimulus with the metronome at 120 strokes per minute (M-120) was not reinforced, and the earlier negative conditioned stimulus with the metronome at 60 beats per minute (M-60) was reinforced with food. No revision occurred. For the entire period of revision the conditioned reflex to M-120 was stronger, on the average, than the conditioned reflex to M-60. In the last experiments, Nos.

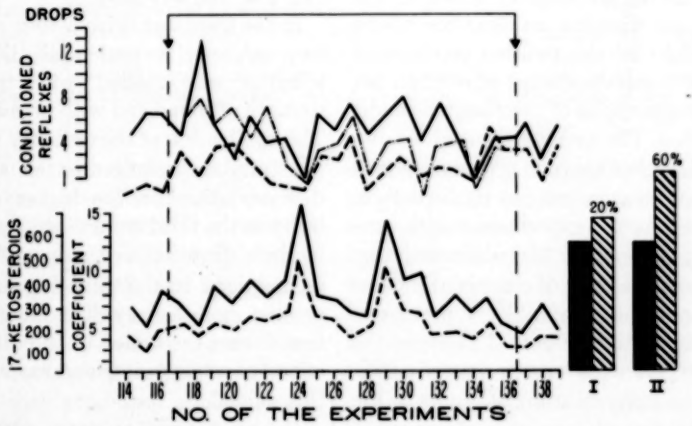

FIG. 2. Second dog. Between arrows—experiments with two-phased revision of signal meaning of M-120 and M-60.

Upper curves: solid line—average height of conditioned reflex salivation to the buzzer and the flickering light; dots and dashes—to M-120; dashes—to M-60. Lower curves: solid line—17-ketosteroids; interrupted line—coefficient.

Columns I—17-ketosteroids; columns II—coefficient. In the control period (experiments Nos. 114–116)—white columns, and in the period of revision—black columns.

135 and 136, the conditioned reflex to M-60 reached an average height equal to that to M-120. In experiments with revision the following phenomena were observed: conditioned reflexes varied sharply, falling to zero, and negativism developed in the dog—it turned away from the food offered to it and even refused it.

The most profound disruption of higher nervous activity was discovered in experiment No. 124. The conditioned reflexes, to all stimuli used, fell almost to zero. A narcotic phase was revealed.

In the majority of the experiments with revision there was noted an elevation of the urinary excretion of 17-ketosteroids, chiefly indicated by the coefficient. The appearance of the almost fully narcotic phase in experiment No. 124 was accompanied by a significantly elevated content of 17-ketosteroids in the urine (to 773 gamma, and the coefficient to 97 per cent).

The use in several successive experiments of the differentiating stimulus with an intensified loudness and a simultaneous prolongation, led to a weakening of the inhibitory process. This was exhibited as bursts of salivation during the time of action of the differentiating stimulus, an elevation of the average height of the positive conditioned reflexes and a certain change of relation between the magnitudes of the positive conditioned reflexes. The means employed for disrupting the higher nervous activity, as well as the consequences, compel us to believe that the dogs in the experiments with prolonged application of the differentiating stimulus were in a state of chronic overstress of the strength of the inhibitory process.

As an illustration, Figure 3 presents the results of experiments with prolonged application of the differentiating stimulus to the first dog. In the experiment of January 17 the height of the conditioned reflexes characteristic for the first dog is shown. In the experiments of January 20, 21, and 22, the differentiating stimulus was prolonged to five minutes, and in the experiments of January 24, 25, 26, 27, 28, and 31 and of February 2 and 3, it was prolonged to ten minutes.

In Figure 3 the columns indicate the magnitude of the conditioned reflex salivation during the entire period of action of the conditioned stimulus; to the positive conditioned stimulus—salivation for 20 seconds; to the negative conditioned stimulus—M-60 (black columns)—for 20 seconds or, in experiments with prolonged application—for five and ten minutes.

Disinhibition by the differentiating stimulus during prolonged action of M-60 was commonly observed as bursts of salivation. With the prolonged action of M-60, in several instances, bursts of salivation lasting for 20 seconds exceeded the salivation for an equal period in response to the positive stimulus, M-120.

The content of 17-ketosteroids in experiments with prolonged application of the differentiating stimulus were elevated in comparison with the preliminary experiments, attaining, during the period from January 20 to February 3, the following amounts: 364, 299, 334, 241, 436, 426, 296, 293, 357, 243, 290, and 241 gamma.

In the third dog, with a very weak inhibitory process, a prolonged differentiating stimulus was applied, with the ordinary strength of sound and with intensified sound. The application of the ordinary differentiating stimulus, prolonged to ten minutes, elicited deviations in the higher nervous activity in the third animal which were similar in their direction to those in the first and second dogs. In the third dog they were expressed more clearly. The bursts of salivation during the action of the differentiating stimulus were greater and more frequent in this animal.

Figure 4 presents the results of experiments with prolonged application of the differentiating stimulus to the third dog. (The symbols in Figure 4 are the same as those in Figure 3.) In the experiment of November 3, which was a preliminary test, the height

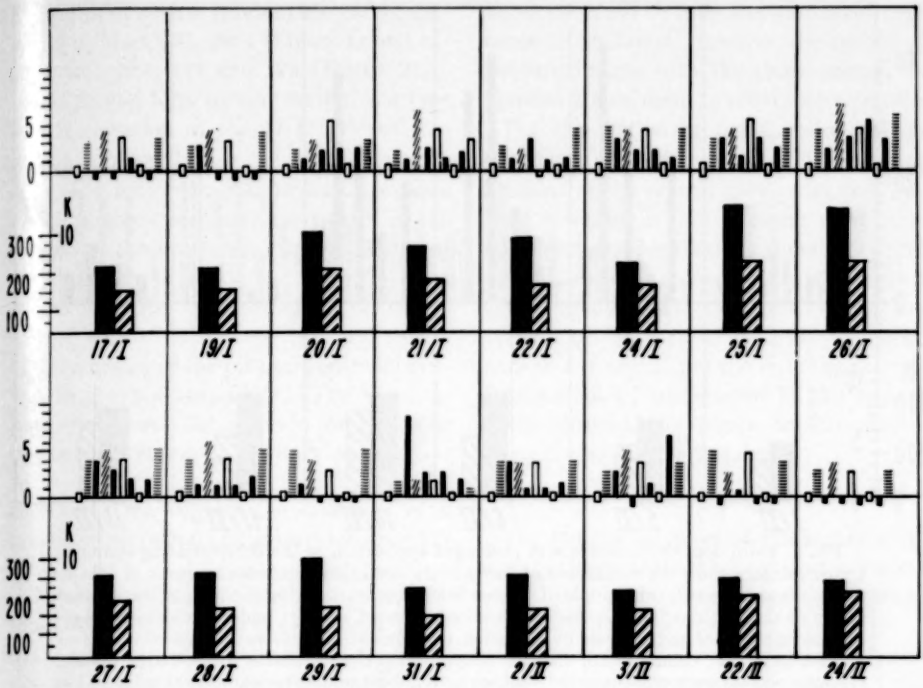

FIG. 3. First dog. From January 20 to February 3, 1955: experiments with prolongation and intensification of the differentiating stimulus.

Upper columns show the magnitude of the salivary conditioned reflexes in drops of saliva; above the abscissa—magnitude of the conditioned reflexes during the time of the isolated action of the stimulus; on the abscissa—brief conditioned stimuli; under the abscissa—conditioned stimuli not accompanied by salivation.

Columns with transverse stripes—conditioned reflexes to M-120; columns with diagonal stripes—conditioned reflexes to the buzzer; white columns—conditioned reflexes to the flickering light; black columns—conditioned reflex to the differentiating stimulus M-60. Lower columns; black—17-ketosteroids in gamma; striped—coefficient for three hours of the experiment.

and relations between the conditioned reflexes were characteristic for the normal higher nervous activity of this animal. In the experiments of November 5, 6, and 10, the dog excreted 330, 442, and 445 gamma of 17-ketosteroids in the urine.

The elevation of 17-ketosteroid excretion in the experimental dogs in connection with revision and with prolonged application of the differentiating stimulus, and in comparison with the control preliminary experiments, is shown in Table 1.

On the basis of the results obtained in the three dogs of various types of nervous system, we have established that an equilibrium between the stimulatory and inhibitory processes in the cerebral cortex in the extra-experimental period is accompanied by a low content of 17-ketosteroids in the urine. In periods of disturbed balance between the processes of stimulation and inhibition there is observed an elevation of 17-ketosteroid excretion.

The obtained results, moreover, indicate the two-fold nature of the reaction of the pituitary-adrenal system in response to a stimulating effect from the central nervous system. The first form of the reaction is a brief, but more greatly elevated, 17-ketosteroid excretion, as noted in our experiments.

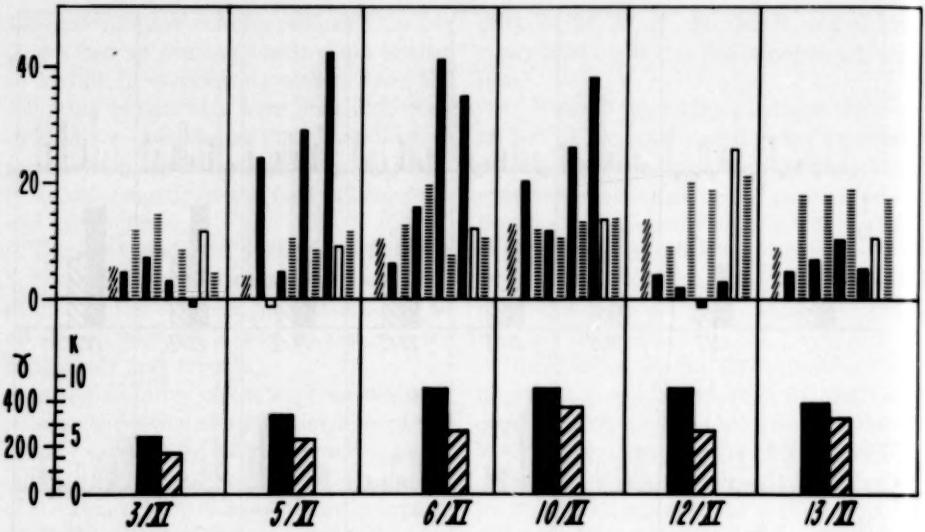

FIG. 4. Third dog. Experiments with prolonged application of the differentiating stimulus. Upper columns show the magnitude of the salivary conditioned reflexes in drops of saliva; above the abscissa—the magnitude of the conditioned reflexes during the time of the isolated action of the stimulus; on the abscissa—brief conditioned stimuli; under the abscissa—conditioned stimuli not accompanied by salivation. Columns with transverse stripes—conditioned reflexes to M-120; columns with diagonal stripes—conditioned reflexes to the buzzer; white columns—conditioned reflexes to the blinking light; black columns—conditioned reflex to the differentiating stimulus M-60. Lower columns: black—17-ketosteroids in gamma; striped—coefficient for three hours of the experiment.

TABLE 1

Summary of Experiments

Dog No.	Type of nervous system	Chronic overstress					
		Strength of the inhibitory process			Mobility of nervous processes		
		N experiments and date	% 17-ketosteroids	Coeff. %	N experiments and date	% 17-ketosteroids	Coeff. %
1	Strong, balanced, passive	12 20/I–3/II 1955 r.	69	52	11 28/V–28/VI 1954 r.	32	47
2	Intermediate among strong, balanced, lively and weak	7 9–18/II 1955 r.	34	183	20 9/XI–6/XII 1954 r.	20	60
3	Strong, unbalanced, lively	3* 5–10/XI 1954 r.	84	90	—	—	—
		7 9–18/II 1955 r.	214	244	—	—	—

* Prolongation of the differentiating stimulus for ten minutes without concurrent intensification of its physical strength.

Examples of such a reaction are the experiments of March 31, 1954 (Figure 1) and experiments Nos. 124 and 129 (Figure 2).

The second form of the reaction is a prolonged elevation of the 17-ketosteroid excretion observed over several successive days, and noticed in the period of revision of the nervous processes (primarily in the periods of the overstress of the strength of the inhibitory process).

There are also certain findings in the literature which indicate the two-fold nature of the reaction of the pituitary-adrenal system to nervous stimulation. The observations of Pincus (23) indicate the existence of a brief elevation of pituitary-adrenal activity, and the experiments of S. N. Nikolaychuk (18) suggest the existence of a prolonged elevation of pituitary-adrenal activity.

These experimental findings, especially those obtained with the third animal, point to the unquestionable elevation of the function of the pituitary-adrenal system in definite instances, and not to the action of other factors. Comparable results obtained in dogs with the aid of the salivary defense and feeding method, indicate that general mechnisms prevail here, which are not connected with the activity of the feeding center alone. If our observations rested on experiments conducted only with the aid of the feeding method, then it might be suggested that the elevation of 17-ketosteroid excretion is connected not with the function of the pituitary-adrenal system, but with the influence of the functional state of the feeding center on the liver, as was shown by M. G. Shmulevich.

The liver, of course, is the site of decomposition of the steroid hormones, and as was shown by Tewell and Freeman (33) in experiments with the reversed Eck-Pavlov fistula, the liver is also the site of decomposition of the corticosteroids. The functional state of the feeding center, stimulating or inhibiting this function of the liver, could indirectly lower or raise the content of hormones in the blood. However, the results of the experiments with the third animal, as reported above, seem to contraindicate this.

The stimulation of the secretion of the anterior part of the pituitary by the higher divisions of the central nervous system appears to occur in the following way: prolonged struggle between the stimulatory and the inhibitory processes in the cerebral cortex, accompanied by overstress of the strength of the cortical inhibitory process, leads to a weakening of the latter and to the development of stimulation in the centers of the hypothalamic region, in turn stimulating the anterior pituitary.

CONCLUSIONS

The functional states of the higher divisions of the central nervous system influence the activity of the pituitary-adrenal system to a marked degree.

Equilibrium and concentration of the basic nervous processes in the cortex of the cerebral hemispheres are accompanied by a low content of 17-ketosteroids in the urine.

A change in the relation between the processes of stimulation and those of inhibition, elicited by overstress of the nervous processes, is accompanied by a significant elevation of the content of 17-ketosteroids in the urine.

Chronic overstress of the strength of the inhibitory process, even in dogs of various types of nervous systems, is accompanied by the highest content of 17-ketosteroids in the urine. In the dog of the lively, unbalanced type of nervous system, the elevation is most prominent.

There is noted a double type of reaction of the pituitary-adrenal system to stimulation by the central nervous system: 1) a transient but great elevation of the urinary content of 17-ketosteroids; 2) a prolonged, less pronounced, elevation of the 17-ketosteroid content in the urine, continuing over several successive days.

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BRIEF COMMUNICATION

CEREBROSPINAL FLUID NEURAMINIC ACID IN PARKINSONISM AND SCHIZOPHRENIA[1]

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The presence of neuraminic acid[3] as a normal constituent of brain gangliosides and its elevation in some neurologic disorders has been reported (2, 5). The cerebrospinal fluid (CSF), being intimately connected with the central nervous system (CNS), may reflect directly any CNS abnormality involving neuraminic acid. Therefore, an investigation was undertaken for the isolation, identification and determination of this compound in control and pathological samples of CSF.

PROCEDURE

By applying column and paper chromatography (7, 8), the presence of both free and bound neuraminic acid were demonstrated in pooled CSF. Bial's orcinol test as modified by Böhm *et al.* (3), used for the determination of total neuraminic acid, is not specific due to the interference of other carbohydrates. This test was used in these studies and appropriate corrections were made for fructose (4) and glucose, both of which are present in CSF. By applying Roe's resorcinol method (6), the range of values reported for fructose was confirmed. It was further found that the resorcinol test was negative for neuraminic acid wheras the Bial's test gave a strong positive color with fructose, nearly equivalent to an equimolar amount of neuraminic acid. Glucose gave a positive Bial's test and although the optical density produced by glucose was low on an equimolar basis with neuraminic acid, glucose is present in far larger amounts than neuraminic acid in CSF, and its interference is significant.

It was found that neuraminic acid, glucose and fructose absorb maximally at 570 mμ and their absorbancies are additive. Reference curves were prepared for glucose and fructose standards by the Bial's test and linearity was observed for the optical range chosen. Each CSF specimen was analyzed for glucose with the glucose oxidase enzymatic method (9); fructose by the Roe's resorcinol method (6) and the total optical density (O.D.) of the two sugars obtained from their standard curves was deducted from the O.D. produced by the Bial's test on a third sample from the same CSF. From the difference of the O.D., the amount of neuraminic acid was calculated by reference to a standard curve prepared with neuraminic acid.

RESULTS AND DISCUSSION

The lumbar CSF was analyzed for glucose, fructose and total neuraminic acid. The results appearing in Table 1 show that the values for glucose and fructose fall in the normal range reported in the literature (4). The values shown for neuraminic acid in CSF were lower than those reported by other investigators (2, 10, 11). A significant elevation of neuraminic acid was found in Parkinsonism, while the controls—patients with non-neurologic disorders—and schizophrenics were found to have much lower

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[3] Neuraminic acid is the unsubstituted compound whose derivatives are known as sialic acids.

TABLE 1
Cerebrospinal Fluid Glucose (G), Fructose (F) and Neuraminic Acid (NA) Mg./100 ml.

Control			Schizophrenia			Parkinsonism		
G	F	NA	G	F	NA	G	F	NA
56.0	4.0	1.8	56.0	3.6	1.2	50.0	2.5	3.3
69.0	4.6	1.8	60.0	3.1	1.1	52.0	3.5	3.3
52.0	2.1	2.2	75.0	4.3	0.8	68.0	3.4	3.5
62.0	3.5	1.6	50.0	2.5	2.7	44.0	3.8	3.1
67.0	2.4	1.8	58.0	3.5	1.6	52.0	5.2	3.3
52.0	3.6	2.4	79.0	2.4	1.4	68.0	4.0	3.0
77.0	4.4	2.2	67.0	2.8	0.6	—	—	—
64.0	3.6	1.9	69.0	3.4	1.5	55.7*	3.7*	3.2*
—	—	—	58.0	4.0	1.8	(±10.0)†	(±0.88)†	(±0.18)†
62.4*	3.5*	2.0*	69.0	2.8	1.4			
(±8.7)†	(±0.88)†	(±0.28)†	—	—	—			
			64.1*	3.2*	1.4*			
			(±9.1)†	(±0.63)†	(±0.58)†			

* Mean values.
† Standard deviations.

values. The elevation of neuraminic acid in CSF in Parkinsonism is of particular interest because in this disorder degeneration of the basal ganglia occurs. The basal ganglia are rich in neuraminic acid containing gangliosides.

The lower values for total neuraminic acid found in these studies, for the controls and schizophrenics as compared to those reported, are due to the fact that no account was taken by these investigators of the glucose and fructose interference in the Bial's test. Consequently, the observation by Bogoch (2) of a deficiency in CSF neuraminic acid in schizophrenics and the conclusions drawn in his report are difficult to evaluate.

Although the range of values for neuraminic acid in the control and schizophrenic CSF appears to be similar, a slightly lower level of neuraminic acid and fructose is seen in schizophrenics when the mean values are compared to the control values. Evaluation of the significance of this difference, however, requires more case studies.

The determination of neuraminic acid in the CSF of patients with Parkinsonism may be a useful adjunct in the diagnosis of this condition.

SUMMARY

Neuraminic acid in the free and bound form was detected in cerebrospinal fluid by chromatography. Analysis of CSF from control, neurologic and mental patients revealed a significant elevation of total neuraminic acid over the control level in Parkinsonism. Schizophrenic fluids contained approximately the same amounts as the controls.

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BRIEF COMMUNICATION

THE RELATIONSHIP OF MENTAL HEALTH TO THE OXIDATION OF N,N-DIMETHYL-p-PHENYLENE-DIAMINE DIHYDROCHLORIDE

R. G. STENNETT, PH.D. AND C. R. CALLOWHILL, PHM.B.[1]

Growing attention has been focused in psychiatry on the possible use of biochemical tests as aids in the diagnosis of mental illness. Recently it has been suggested that the metabolism of epinephrine and other amines may be altered in schizophrenia. Akerfeldt (1), for example, has claimed that the fresh blood serum from mentally ill patients has the capacity to oxidize N,N-dimethyl-p-phenylene-diamine (DPP) more rapidly than fresh serum from healthy control subjects. He suggested that this increased oxidizing activity of the patient's serum was probably due to an increase in the level or activity of ceruloplasmin (a copper-containing enzyme) in the patient's serum and a decrease in the ascorbic acid content. Ascorbic acid was identified as accounting for 95 per cent of the substance in serum capable of reducing the oxidation of DPP. Akerfeldt, as well as most other workers, noted that the DPP oxidation test is not specific for mental disease.

The present study was undertaken to provide additional data in terms of which the practical psychiatric use of the Akerfeldt test might be evaluated. Special features of this experiment include: 1) very careful matching of patients and controls with respect to age and sex, 2) a refinement of the usual patient-control dichotomy by the use of a battery of psychological tests, 3) selection of the patient sample to provide age-sex balanced groups of two different diagnostic entities, and 4) elimination from the study of any persons with significant somatic illness.

It was not possible, unfortunately, to institute control of the ascorbic acid intake of our subjects or to measure their serum ascorbic acid levels. We felt, however, that our institutional diet was adequate in this substance.

METHOD

Subjects: Group 1. The *Ss* in this group were eight male and eight female patients who were matched for age, with eight male and eight female ward staff who served as control *Ss*. Eight patients were diagnosed as suffering from paranoid schizophrenia and eight were catatonic schizophrenics. Each of these diagnostic categories was represented equally by sex. All *Ss* were carefully selected from larger numbers so that all were English-speaking, had Grade 8 education or better and were between the ages of 20–55. No *S* was suffering from any somatic disease and all patients used were taken off any form of treatment well in advance of the testing procedures.

Subjects: Group 2. An additional group of 16 patients and 16 controls were selected in the same way as Group 1 except that the criteria of age limits, education and language were not required.

Procedure: Akerfeldt Test. The fasting blood samples, collected in vacuum tubes, were treated according to Akerfeldt's original procedure. One and a half c.c. of a fresh solution of 0.1 per cent N,N-dimethyl-p-phenylenediamine di-hydrochloride (DPP)

[1] Ontario Hospital, St. Thomas, Ontario, Canada. This study was performed under the direction of Dr. C. A. Cleland, Superintendent, with the advisory participation of Dr. J. F. Cawthorpe and Dr. R. D. Whiteside. The authors would like to express their appreciation to the ward staff of the Ontario Hospital, St. Thomas, for their cooperation in serving as control subjects for this experiment.

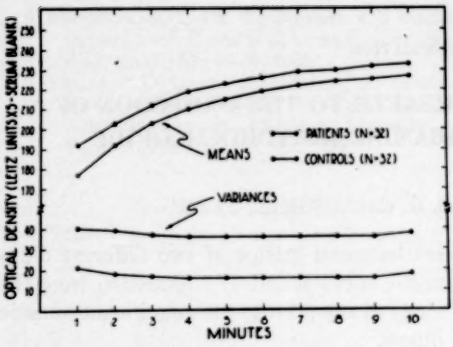

FIG. 1. Means and corresponding variances of optical density over the 10 min. test period for 32 patients and 32 control *Ss*.

were added to 1.5 c.c. of serum. Optical density was read on a Leitz Photoelectric Colorimeter, "zeroed" with a water blank and using filter "A." Readings were taken each minute for 10 min. both with a reagent blank made of 1.5 c.c. water and 1.5 c.c DPP and a serum blank made of 1.5 c.c. serum and 1.5 c.c. water. (The above procedure was also used with the Coleman Jr. Spectrophotometer, "zeroed" with a water blank and set at a wave length of 550, when subsequent checks of the Leitz machine and our laboratory procedures were conducted.)

Psychological Tests. Immediately after the blood samples had been taken all *Ss* in Group 1 were given a battery of psychological tests. These tests were: The Vocabulary and Block Design subtests of the Wechsler Adult Intelligence Scale (WAIS); the Bender Gestalt (BG) test with a memory section (BG Mem); the Tendler Word Association Test (T1 to T5) and the adult's and children's version of the Differential Diagnostic Technique (DDT and CDDT). The latter two tests are drawing tests which, for the purposes of this experiment, were used as a refinement of the BG. The complete battery of tests produced 11 scales all measuring different aspects or dimensions of ego control or mental health.

RESULTS

Psychological Tests. Of the 11 variables derived from the test battery, six gave rise to statistically significant patient-control differences in the predicted direction. The other five were in the expected direction but did not reach the usual significance levels. In general, it was quite apparent from test data that our samples of *Ss* were drawn in such a way that great differences in mental health existed between them (3).

Akerfeldt Test Results. Curves describing the 10 min. time course of the Akerfeldt reaction are shown in Figure 1.

Each point on the upper two curves is the mean value for either 32 patients or 32 controls. Each point on the lower curves is the variance of the corresponding mean.

A finding of note is that serum density is correlated $-.794$ ($P < .01$) with the 10-min. Akerfeldt (reagent-blank) values. This is reflected in the fact that the 1 min. Akerfeldt values taken with a reagent blank correlate only .510 ($N = 64$), with the 1-min. Akerfeldt values taken with a serum blank.

A comparison of 1-min. Akerfeldt, serum-blank values of the 32 patients and 32 controls produced a t value of 1.03 which is not statistically significant. A correlation of a composite mental health score derived from the psychological test battery with the 3-min. Akerfeldt, reagent-blank values also did not reach usual statistical significance levels ($r = .097$; $N = 32$).

A comparison of the 6-min. Akerfeldt, reagent-blank values for the 16 paranoid and 16 catatonic schizophrenics yielded a non-significant t value of 0.111. The 6-min. Akerfeldt, reagent-blank values of the 18 patients who had been hospitalized for more than three years were compared with the corresponding values of 14 patients hospitalized for longer than 3 years and the resulting t value (0.533) was not significant. A correlation of age against 3-min., Akerfeldt, reagent-blank values, however, turned out to be .297 which is significant at the 5 per cent level of confidence.

SUMMARY

Comparison of DPP oxidation curves of carefully-matched groups of schizophrenics

and controls failed to reveal statistically significant differences. DPP oxidation is unrelated to mental illness *per se*, sex, length of hospitalization or differential diagnosis; it is related significantly to age and serum density.

These results suggest, in agreement with Horwitt (2), that the Akerfeldt reaction in its present form is so easily contaminated by nutritional and other artifacts as to render it useless as a practical aid in psychiatric diagnosis.

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BRIEF COMMUNICATION

OBSERVATIONS ON THE HOPKINS-COLE REACTION IN THE URINE OF SCHIZOPHRENICS

BERNARD S. HELLINGER, M.D.[1] AND M. RICHARD PACHTER, M.D.[2]

Evidence for a metabolic disturbance in schizophrenia has been sought in studies of the excretion of aromatic amino acids and their products, including tryptophan and related indoles (4, 9, 10). Riegelhaupt reported that the glyoxylic acid reaction (Hopkins-Cole) for the tryptophan group gave positive results in the majority (78 per cent) of urines from 65 schizophrenics and negative results in the majority (74 per cent) of urines from 67 non-schizophrenics including 12 normals. Attempts to confirm the above results prompted the present paper.

MATERIAL

Urine specimens were obtained from 32 recently hospitalized schizophrenic patients and 209 non-schizophrenics. The latter included 125 adults and 69 children hospitalized for physical illnesses, two healthy adults and 13 adults hospitalized for mental disorders other than schizophrenia. These were: four character disorders, two depressive reactions, two involutional psychoses, two alcoholic psychoses, one psychotic depression, one acute brain syndrome and one pathological intoxication.

Eleven of the schizophrenics and one patient with a non-schizophrenic psychotic depression were receiving chlorpromazine.

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[2] Henry Ford Hospital, Detroit, Michigan.

METHODS

The Hopkins-Cole procedure as described by Riegelhaupt (10) was followed. The urines were collected as single, mid-morning specimens and tested within six hours. Two ml. of filtered urine was well mixed with 1 ml. of glyoxylic acid solution, and then 1 ml. of concentrated sulfuric acid was allowed to flow slowly, over a period of 20 seconds, down the side of the test-tube. A positive reaction consisted of a violet color at the interface.

The Hopkins-Cole test was also performed on aqueous solutions of chlorpromazine and urine specimens to which chlorpromazine was added.

RESULTS

Positive Hopkins-Cole reactions were observed in only a small percentage of specimens from patients in all of the groups not receiving chlorpromazine (Table 1). Among such chlorpromazine-untreated patients there were positive reactions in only three of the 21 schizophrenics (14 per cent), four of the 12 nonschizophrenic mental patients (33 per cent), 17 of the 69 somatically ill children (25 per cent), 13 of the 125 somatically ill adults (10 per cent), and in neither of the two healthy adults. On the other hand, positive reactions were obtained in all 12 of the specimens from the 11 schizophrenics and the one nonschizophrenic psychotic depressive receiving chlorpromazine. Furthermore, when chlorpromazine was added to urine specimens, a positive reaction was observed in every case. Positive reactions were always observed in aqueous solutions of chlorpromazine.

DISCUSSION

We were unable to confirm Riegelhaupt's finding that positive Hopkins-Cole reactions of the urine are observed in specimens from a majority of schizophrenic patients.

Only three positive reactions were observed in the specimens of 21 schizophrenics not receiving chlorpromazine (14 per cent). Positive reactions were observed in specimens from 34 of the 208 non-schizophrenics not receiving chlorpromazine (12 per cent).

Riegelhaupt noted a lack of clarity of the reaction in the urines of patients receiving chlorpromazine and classified such results as doubtful unless the colors characteristic of a positive reaction were clearly discernible.

We observed positive reactions which were characteristic in color and often intense in all specimens from patients receiving chlorpromazine and these results were set aside. They were apparently due to chlorpromazine since positive reactions were observed when chlorpromazine was added to urine specimens and with chlorpromazine in aqueous solution.

It should be noted that our schizophrenic patients were recently hospitalized while Riegelhaupt did not describe his patients in regard to duration of hospitalization or of illness. We used midmorning urine specimens. Riegelhaupt used morning urine specimens and did not specify whether these were the first specimens voided (overnight urine). Such differences might contribute to the difference in our findings.

In an attempt to elucidate the problem further, two modifications of the usual Hopkins-Cole procedure were introduced. First, the urine specimens were diluted in an attempt to decrease the visual masking effect of deeply colored urines upon the violet ring of a positive reaction. Previously negative specimens from the two healthy adults were observed to give positive tests after dilution. Second, a more concentrated Hopkins-Cole reagent was used, which was sensitive to a lower concentration of tryptophan than the original reagent (5). Specimens from eight schizophrenics and 27 non-schizophrenics were tested with the sensitive reagent and all of the specimens from the schizophrenics and 23 from the non-schizophrenics were positive. Dilution of the "negative" specimens increased the number of positives to 26 and on repeat testing the following day a specimen from the 27th individual was also positive.

TABLE 1

Results of the Hopkins-Cole Test

Diagnoses	No. of Patients	No. of Positive Specimens	% Positive Specimens
Schizophrenic			
No chlorpromazine	21	3	14
Receiving chlorpromazine	11	11	100
Non-schizophrenic mental disorders:			
No chlorpromazine:	12:	4:	33:
Acute brain syndrome	1	0	
Character disorder	4	2	
Depressive reaction	2	0	
Involutional psychosis	2	1	
Alcoholic psychosis	2	0	
Pathological intoxication	1	1	
Receiving chlorpromazine:	1:	1:	(100)
Psychotic depression	1	1	
Physically ill:			
Adults	125	13	10
Children	69	17	25
Healthy Adults	2	0	0

Normal excretion rates for tryptophan have been given various values by various authors ranging from 10–45 mg. per day (2, 6) to about 280 mg. per day (1). Varying the sensitivity of the Hopkins-Cole test in relation to the normal excretion rate should vary the percentage of positive reactions accordingly and this would explain the high percentage of positive reactions observed in our later work.

It is suggested that further studies of tryptophan and related indole excretion should be quantitative in nature. The subject's age, sex, weight, drug and dietary in-

take and volume of urinary output should be known and quantitative chemical determinations should be made.

SUMMARY

We were unable to demonstrate any correlation between a positive Hopkins-Cole reaction of the urine and the presence of schizophrenia. About one-seventh of the specimens from both schizophrenics and non-schizophrenics were observed to be positive. Positive Hopkins-Cole reactions were always observed in the urines of patients receiving chlorpromazine (so that the test does not appear specific for the tryptophan group). In further testing with a more sensitive Hopkins-Cole reagent and dilution of the specimens to decrease the masking effect of urinary chromagens, all but one of the specimens from both schizophrenics and non-schizophrenics, including 18 normals, were positive. It is suggested that further studies of tryptophan and related indole excretion should be quantitative in nature.

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BRIEF COMMUNICATION

INVESTIGATIONS ON THE TRYPTOPHAN CONTENT OF URINES FROM SCHIZOPHRENICS AND OTHER PSYCHOTIC PATIENTS

E. L. EDELSTEIN, M.D.[1] AND D. KRASSILOWSKY, M.D.

Research workers have been stimulated by the fact that, though inconsistently, numerous minor physiologic abnormalities have been found in schizophrenia. These findings and certain clinical features may all point to the organic nature of the disease and a specific metabolic deviation would fit into a genetic scheme (8). Indole metabolism is gaining more attention than ever, because of the research done on the hallucinogenic drugs, all of which contain the indole nucleus.

Sano (10) found among 1500 mental patients that the Indican excretion in schizophrenia was abnormally high. McGeer *et al.* (6) reported chromatographic studies which indicated the presence of more diazo-coupling compounds in the urine of schizophrenic patients than in normals. She later found a physiologic alteration in the excretion of aromatic compounds, which however could be controlled by a suitable diet (7). Horwitt *et al.* (4) also stressed the dependency of indole levels in urines on dietary sources.

Riegelhaupt (9) investigated the presence of amino acids and their metabolites in urines of 120 psychotic patients, by using the Hopkins-Cole reaction, also known as the glyoxylic acid test, for the presence of tryptophan. Using this simple color reaction, he obtained positive results in 78 per cent of urines of 65 schizophrenic patients, while the majority of non-schizophrenics (74 per cent) showed negative results. The simplicity of the procedure and the highly significant results obtained led us to replicate this study on our in-patient material.

MATERIAL

Urine samples of 77 heretofore untreated patients were examined. Thirty-two were schizophrenics (16 of the simplex type, seven paranoid, one catatonic and eight of the chronic type). Ten patients were diagnosed as manic-depressive psychoses, five involutional psychoses, one post-partum psychosis, one senile dementia, three organic psychoses, one epileptic, 20 variously neurotics and four psychopaths. The national origin of this group was notably varied, as they came from 12 different countries. The average age of the schizophrenic group was 27 years.

As normal controls 21 members of the hospital staff were examined. On another and later test series, urine samples of 23 patients already under insulin shock treatment were examined. They had received 10–32 comata, achieved by various insulin doses, ranging from 40–570 units. Saving one, all these patients were schizophrenics.

METHODS

The technique of the glyoxylic acid reaction was exactly that used by Riegelhaupt (9). Urine samples, not containing albumin, voided in the morning, were tested about two hours later. Two ml of filtered urine were well mixed with 1 ml of gyloxylic acid. Then 1 ml of concentrated sulfuric acid was allowed to flow slowly—approximately within 20 seconds—down the side of the test tube, thus allowing a sharply de-

[1] The Psychiatric Hospital "Talbieh," affiliated with the Medical School, Hebrew University and Hadassah, Jerusalem, Israel. The authors acknowledge with thanks the help of the directors of "TEVA" Middle East Pharmaceutical & Chemical Works, Ltd. in supplying the necessary reagents for this study.

fined layer to form beneath this mixture. When stratified in this manner a positive finding is indicated by a reddish-violet colored layer forming at the zone of contact of the two liquids.

We also applied a different test, recommended by Abelin (1) as specific for tryptophan, not linked to polypeptides. It consists of letting 2 ml of ethylacetate or amylalcohol flow down the side of a test tube containing 3 ml of urine and then adding Bromwater drop by drop. In the presence of tryptophan, a red or violet coloration appears, which passes over into the layer of ethylacetate or amylalcohol on shaking the tube.

In addition, we attempted to determine the quantitative excretion of tryptophan. Utilizing the same color reaction, we prepared standard solutions of tryptophan as well as blanks in the same acid solution, as tryptophan is quite stable when digested with acid (5). After shaking up the ring the same violet color diffused throughout the whole test tube. After cooling, the samples were compared to standard solutions in Klett's Electrophotometer using a red filter. Normal urines, *i.e.* negative glyoxylic acid reactors, could not be compared with the positive ones colorimetrically, as their color with the reagent was of quite a different nature, displaying a brown or reddish tinge. Various organic solvents used in order to extract these colors and to discover traces of violet hues did not lead to any positive result.

RESULTS

Of the 77 pathologic cases, ten (13 per cent) gave a clearly positive glyoxylic acid reaction. Another 15 per cent had doubtful reactions. The percentage of positive reactions within the schizophrenic group was 21.8. All normal controls were negative.

Of the series of 23 patients under insulin shock treatment, positive glyoxylic acid reactions were found in three cases, with two more cases of doubtful quality.

Using Abelin's method for non-polypeptide-linked tryptophan on the same urine samples, all results were completely negative.

Those urine samples having given positive results were subjected to quantitative measurements and yielded results varying between 432 mg to 1505 mg per 24 hours amount of urine. Total amounts of tryptophan excretion in normal subjects has been stated as a mean value of 41.4 mg per 24 hours amount of urine (12).

DISCUSSION

Contrary to Riegelhaupt's findings, our data revealed no significant positive results of the glyoxylic acid test on the urines of schizophrenic patients. Less than one-quarter of the untreated schizophrenics gave a positive color reaction. It should be noted that Frohman *et al.* (3) showed that increased tryptophan excretion was not specifically associated with schizophrenia.

Tryptophan is the precursor of nicotinamide as well as of serotonin in the human body (11). Pigments derived from tryptophan include representatives of two classes (2): 1) indigoids, formed by the actions of halogens or other oxidizers on free tryptophan, and 2) pigments of the Hopkins-Cole type, formed from free or peptide-linked tryptophan by condensation with aldehydes and subsequent oxidation. Some aldehydes or aldehyde-containing substances (formalin, benzaldehyde, vanillin, glyoxylic acid) produce a characteristically violet color with tryptophan in the presence of concentrated mineralic acids. This reaction might be used for the recognition of tryptophan. Although the exact nature of the chemical process is not understood clearly as yet, one possibility seems to be the reaction of the aldehyde oxygen with the hydrogen of the α-indole carbon.

SUMMARY

The glyoxylic acid reaction (Hopkins-Cole reaction for tryptophan) on urine

samples of psychotic patients gave positive results in seven of 32 schizophrenic patients and in ten of 77 of all mental patients. All normals gave negative results.

The data obtained from patients under insulin shock treatment did not vary significantly from those obtained from untreated patients.

No positive results could be obtained in the urine samples of any of the schizophrenic patients by the method with Bromwater, described as specific for non-peptide linked tryptophan.

The tryptophan level in those samples giving a positive test result was very much higher than is assumed to be normal.

Possible factors responsible for the reactions are briefly discussed.

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COWDRY, E. VINCENT, ED. *The Care of the Geriatric Patient*. C. V. Mosby Co., St. Louis, 1958. 438 pp. $8.00

Few authors or editors deserve or will get a wider audience in geriatrics than Professor E. Vincent Cowdry. His many years in the field have not dimmed his viewpoint nor abated his capacity for intellectual counterpoint. In his initial pages there is an immediate challenging restatement of his forceful proposals for adequate categories of geriatric education. Such positive attitudes have become the hallmark of this vigorous dean of the field of aging. These subjects have not diminished in controversy during the past five years, and quite probably a more respectful attitude from the opposition has been obtained by his espousal. A majority of those in the clinical world are opposed to organized special study in geriatrics. There is no difficulty in defending this traditional attitude, but such inflexibility does not necessarily make the minority viewpoint thereby incorrect.

The book is a catalogue that outlines the form of a clinical science as it emerges from a great deal of collateral data. It is of the compendium variety, with twenty-two contributors, of whom more than half have been identified in distinguished fashion with the clinical and social fields of aging. The nineteen chapters, each with its key bibliographic items and capped by a good volume index in a competent and handy publishing package, fall roughly into a first half of clinical, and a second half of social, features. As such, it is a satisfactory panorama of mid-twentieth century attitudes on aging in the culture of western nations. Generally the book is a broad educational outline of facts by which to initiate the uninformed and with which to prompt the memory of those engaged in the field.

It is important to point out that the title word "care" must not be assumed to imply "medical care." This distinction indicates that this is not a textbook in geriatrics. It is more in the nature of a useful hybrid of clinical, social, and general considerations of aging. As a matter of fact, some of the medical textual chapters are not equal to chapters by Randall, Donahue, Bluestone, Tibbetts, and Sheldon, who are gerontology veterans of years' standing.

In such collections of sequential essays, it probably would not be fair to criticize material which has been based on reading and opinion rather than clinical observations. On the other hand, there are sentences which are valuable clinical contributions, *viz.*, "too often in the aged the question is not so much whether the patient can survive surgery, but whether he can survive without it" (Orr). For the most part the book is an affirmation of known theses by authorities which can serve to refresh those who know the field, and to stimulate those who have not been aware of the tenacity and intelligence of workers who now must be considered, possibly to their embarrassment, as pioneers.

Views on the case for the need for specific medical education in geriatrics crop up in several chapters. Dr. Cowdry offers no compromise: education in geriatrics cannot be left to "internists now in practice who received their medical education some years ago, when the problems of aging were, for the most part, simply ignored." Possibly seeking to gain half an educational loaf, Dacso suggests the use of a medical coordinator to channel all training in aging from preclinical to clinical years. As a part of a comprehensive collection of world-wide appraisals of geriatric problems by Tibbetts and by Sheldon, the field of social medicine is sketched out with economy and acumen. The latter feels that "... the care of aged

and chronically ill persons can no longer be left to chance, but requires the presence of individuals with special training and interest. . . ." This phrase is reminiscent of the tart statement: war is too serious a matter to be left only to the generals.

Despite the general informative value of the book, there are certain debits. In some of the clinical chapters particularly, there is an absence of formality, and a certain lack of depth of observation which is distracting. Specialists from other fields do not become specialists in geriatrics by the citation of authoritative statements. Interlineations of inadequate observations cannot be passed off uncritically. Secondly, there can be no place in an important scientific work for unhappy terms such as "oldster," "senior citizens," the unrealistic phrase "golden age," or "sunset years." To record that the term "old codger" was used is criticism enough. Lastly, the able and distinguished Dr. L. Z. Cosin of England deserves to have his name spelled correctly. Few in his country have excelled his energy, initiative, and ability.

All in all, there is too much useful material to permit lesser and remediable trivia to weigh against the book as a whole. For many, students, workers, and particularly educators, there is much that can be scanned with ultimate benefit to that fraction of the population for which, in the last analysis, all of these efforts have been made.

Joseph T. Freeman

BRODAL, ALF. *The Reticular Formation of the Brain Stem.* Charles C Thomas, Springfield, Ill., 1957. vii + 87 pp., illus. $3.00

JASPER, H. H., PROCTOR, L. D., KNIGHTON, R. S., NOSHAY, W. C. AND COSTELLO, R. T., EDS. *Reticular Formation of the Brain.* Henry Ford Hospital International Symposium. Little, Brown & Co., Boston, 1958. xiv + 766 pp., illus. $16.00

In the last few years a great proportion of neurophysiological investigation has been concentrated on certain behavioral problems the study of which was encouraged, if not made possible, by the classical observations of Magoun and Moruzzi. Their initial work on the reticular activating system opened a new area to physiologists, psychologists, pharmacologists and others interested in problems of behavior and particularly in the changes which take place in the brain when one's attention is aroused, when one becomes alerted or when it becomes necessary to alter the degrees of one's "awareness" under various circumstances. In other words, a major step forward was made in regard to the understanding of the neurological basis or concomitants of behavior.

No sooner was this vast field made available than it became apparent that a number of anatomical problems were at hand. Some of the older neuroanatomy would have to be reassessed and new studies would have to be carried out dealing in large part with those areas of the brain stem (and presumably related areas at higher levels) to which the name "reticular formation" had been given before the turn of the century. In his small monograph, Professor Brodal has attempted to summarize recent work, with particular reference to studies carried out in the Department of Anatomy at the University of Oslo, dealing with fiber connections of the reticular formation, and on this basis to suggest some principles of the organization of this complex area of the central nervous system. His work is primarily concerned with the brain stem (as comprising the medulla oblongata, pons and mesencephalon) since as he states, ". . . it is uncertain whether the so-called reticular nuclei of the diencephalon are homologous to the reticular formation of the mesencephalon, pons and medulla." There is no

point here in discussing the beautiful detailed anatomical findings which are limited to a certain extent by the techniques available. Although a number of important observations have been made many questions still remain to be answered, such as the site and mode of termination of reticulospinal fibers; the distribution within the reticular formation of collaterals from the secondary ascending fibers (these may be of particular importance in relation to drug effects); the topography of the connections between lateral and medial areas of the reticular formation, etc.

It is of considerable interest, however, that a number of physiological observations are compatible with the conclusions derived from the anatomical studies. Dr. Brodal comes to the conclusion that, "The reticular formation is subdivided into several regions which differ with regard to their cytoarchitecture, fibre connexions and intrinsic organisation. These regions, however, cannot be considered as being independent of each other, since their fibre connexions provide ample possibilities for interaction and collaboration between the various regions. The anatomical data suggest that certain generally accepted notions of the functional organisation of the reticular formation are in need of revision."

One of the major suggestions made is that future physiological investigation will have to take structural factors more into account than has been the custom hitherto. That such is indeed the case is demonstrated by much of the discussion presented in the Henry Ford Hospital Symposium at which Professor Brodal unfortunately was not present. His work is substantiated by the findings of Nauta and Kuypers who present their latest analysis of the ascending pathways involved in the reticular formation. They specifically demonstrate a major pathway which ascends throughout the length of the brain stem tegmentum as a component of Forel's tractus fasciculorum. Its axons originate in the medulla and pons and are distributed to extensive regions of the tegmental reticular formation, the periaqueductal gray matter, superior colliculus and pretectal area, intralaminar thalamic nuclei and subthalamic region. Associated with it via an intermediate reticular path, is a lateral tegmental fasciculus. An extensive mesencephalic region projects to the hypothalamus, preoptic area and medial septal nucleus. Together with the limbic system, with which it is reciprocally connected, it appears to represent a neural mechanism of homeostatic control over endocrine and autonomic functions.

Further anatomical work is presented by Scheibel and Scheibel dealing with the fine structure of the reticular formation. All of these beautiful studies demonstrate the presence of a central internuncial system which is extremely complex and organized to a very high degree. "Its input consists not only of sensory collaterals, but also of axons descending from higher centers, all orderly and precisely arranged. This output is directed both downward and upward, in the latter case ending predominantly in the diencephalon."

On this structural basis an outstanding series of papers is presented dealing with physiological, pharmacological and behavioral problems, concepts and observations which, although integrative in goal, revolve around the central role of the reticular formation. Space does not permit any extensive detailing. Suffice it so say that every one of the papers will be of interest and value to anyone working with the nervous system and behavior. A number of general problems appear here, however, which are of wide significance, and perhaps more than any other single factor demonstrate the value of such a symposium. The fact that the reticular formation has many inputs and outputs, rich synaptic connections and single axons going from a given cell both up

and down the neuraxis, and many kinds of cells, makes it necessary to think of a large number of variables in attempting to understand and interpret its functional organization. These variables, affecting different groups of cells and fibers in the complex, include such factors as specific excitatory and inhibitory properties, sensitivity to drugs, responses to self-stimulation, and a host of others discussed, with his usual acuity and perception, by Dr. Gerard in the final summary. The new data makes it almost necessary to think of altering many of the classical, fundamental ideas about the way the central nervous system works, and gives one the feeling that perhaps the area has finally appeared through which neurophysiology will be able to make the contribution to the understanding of the mechanisms of behavior which, for many reasons, has been delayed so long. Questions arise concerning unitary consciousness combined with specificity and differentiation of attention; of synaptic and other integrative mechanisms touching upon temporal and spatial integration; and a host of derivative questions as one follows this lead. Information handling (coding), problems of redundancy, channel capacity and overloading, feedback and reverberation all must be considered—many in a new light—as a result of these discussions. In any case the present flourishing of neurophysiological, neuropharmacological and neurochemical investigation related to and stemming from the fascinating problems raised by the structure and function of the reticular formation, may be the beginning of a new era in the understanding of the behavior of the total organism.

It will have been obvious from what has been said above that both the volumes are invaluable. It may be added that in both cases the publishers have also carried out their part of the venture extremely well.

ROBERT G. GRENELL

FREEMAN, THOMAS, CAMERON, JOHN L. AND MCGHIE, ANDREW. *Chronic Schizophrenia.* International Universities Press, Inc., New York, 1958. x + 158 pp. $4.00

In the reviewer's opinion, this rich little book will prove to be an enduring contribution to the literature on chronic schizophrenia.

It reports the results of an endeavor, investigative but explicitly therapy-oriented, which the authors pursued over the course of two years at the Glasgow Royal Mental Hospital. They set up a special treatment center, in an institution which evidently until then had been oriented along Kraepelinian lines, for the purpose of studying the problems presented by the chronic hospitalized schizophrenic patient. Twelve female patients and six male patients were selected to live on this unit, and certainly their illnesses were so formidable as to constitute an acid test of the therapeutic measures which came to be employed in their behalf. Among the women, the average duration of illness was eight years; among the men, nine years. By the standards of, say, the state hospitals in this country, each of these patients would be considered to have a hopeless prognosis.

Three methods of study were used concurrently: 1) group therapy, 2) observation of the interaction on the (female) patients' ward, and 3) the arrangement of a day-room where the patients spent their whole day, provided with various occupational material, and in the company of experienced nurses who worked in close collaboration with the authors. The group therapy, although continued throughout the study, soon proved to be yielding less of therapeutic results than the investigators had hoped for, and they then turned their main therapeutic effort, with impressively good effect, toward fostering the patients' establishment of healthy identifications with the nurses in the day-room. The authors clearly and consistently show this

treatment-measure to be an outgrowth of their basic theoretical tenet, which they italicize:

"... *It is this factor of 'ego feeling,' or the ability to differentiate the self from the environment, that we regard as being damaged in chronic schizophrenia, thus leading to the patient experiencing internal and external sensations as a continuum. We believe that, once this basic disturbance is appreciated, all other schizophrenic manifestations can be viewed as necessary elaborations of it*" (p. 51).

Opening their book with an excellent review of the contributions to the understanding of schizophrenia by Freud and his followers, as well as by such deviants as Klein, Fairbairn and others, the authors then pursue the ramifications of the above-described central theme through a number of well-dovetailed theoretical chapters which cover such subjects as confusion of identity and disturbances in perception, thinking, and memory. All these chapters contain observations which are sufficiently new and stimulating to be of value not only to the clinician, but to any one who is doing research in these areas. The authors show not only a considerable ability in the handling of theoretical matters, but an outstanding grasp of the subtleties of clinical phenomena. Their observations of patients' confusion of identity, and of early indications of patients' identifying with their nurses, are masterly; I know of no book on schizophrenia which gives more perceptive and vivid clinical vignettes.

The book's main deficiency is that it conveys an oversimplified impression of the psychodynamics, and necessary psychotherapy, of schizophrenia. This is no doubt due, in part, to the circumstance that the authors were working with extremely deeply ill patients, patients whose schizophrenic break had occurred long ago and who had reached, by the time these investigators began working with them, a level of extreme dedifferentiation. The authors themselves are aware of, and comment upon, the degree to which long-continued schizophrenia impoverishes the personality: noting how similar are the thumbnail sketches of their eighteen patients, they comment, "It is our contention that loss of individuality is a feature of the chronic patient in the refractory ward." It seems to me likely that this relative simplification of personality structure may tend to give rise to a comparably simplified theory. The authors' basic tenet, as to the loss of ego-boundaries in chronic schizophrenia, would I think soon be highlighted, when applied to an understanding of acute schizophrenia, to be a useful key, but not *the* key which it is here portrayed. As long as it is quite clear that they are referring to *chronic* schizophrenia, this objection is a mild one; but the book does tend to leave an impression that schizophrenia as a whole is to be understood by using this one key alone.

As I see it, the dissolution of ego-boundaries is a defense of the personality—albeit a last-ditch one—against intense anxiety from whatever source, and the sources can be as manifold as the complexities of human living itself. Where the authors treat this symptom almost as if it were the prime causative agent of schizophrenia, it would seem more accurate to view it as being indeed a symptom, about which the patient is—as with all symptoms—deeply ambivalent. Therapeutic efforts might better be predicated upon the assumption that although something in him wishes to be cured of this symptom, something else in him will fight against relinquishing what is experienced as an urgently needed defense against overwhelming anxiety—anxiety referable to dissociated murderous feelings, incestuous feelings, grief, tender feelings, and so on. This matter of the causality of schizophrenia is surely a formidable problem; but we know enough about this—from, to cite but one among many writings about this subject, the book entitled *Psychotherapeutic Intervention in Schizophrenia*, by Lewis B.

Hill—to warrent a stronger statement about causality than the authors make:

"We have consciously ignored any aetiological implications in discussing our views on schizophrenia, although fully aware that, accepting the conclusion that a schizophrenic state is essentially one of dissolution of the ego, we are still faced with the question as to causality.... Our present knowledge of physical and psychical processes and the correspondence between them renders, in our opinion, any aetiological explanations purely hypothetical and possibly misleading" (p. 136).

But within the limits which I have described—limits which, for the most part, the authors themselves clearly acknowledge—this is an excellent book. It deserves, in fact, to become one of the standard, regularly consulted works on schizophrenia. It offers, in small space and highly readable style, much that is useful to a wide range of workers in this field; researchers and teachers, therapists, administrative psychiatrists, and ward-personnel. The treatment results which the authors report, from their facilitating of the patients' forming healthy identifications with nursing personnel, are sufficiently promising to warrant serious consideration, and in my opinion emulation, by all persons charged with the treatment of chronic schizophrenia. This measure would seem to be valuable not only in lieu of intensive individual psychotherapy, as was the case here, but also as a prelude to, and concomitant of, such psychotherapy in institutions where the latter is available.

Harold F. Searles

LIEBMAN, SAMUEL, ED. *Understanding Your Patient.* J. B. Lippincott Co., Philadelphia, 1957. 170 pp. $5.00

The seventh Annual Lecture Series of the North Shore Hospital in Winnetka, Illinois, has been compiled into this small volume. These lectures were designed to aid the medical practitioner in gaining an increased understanding of the various emotional problems he may encounter in his patients. This book is not written for the psychiatrist or for anyone who seeks a detailed account of human development and behavior. However, the nine well-known contributors offer in a succinct and lucid fashion a discussion of the many problems of childhood, adolescence and adult life, including premarital and marital counseling. One of the lectures devoted to the role of grandparents is of interest. Also of note is a chapter by Dr. Lauretta Bender in which she discusses psychotic reactions in children. While psychotic reactions are considered rare in children, they are more frequently being recognized and the useful, but perhaps not widely known material presented by Dr. Bender may enhance the practitioner's awareness of these psychoses as they occur in children.

This book should supplement the busy practitioner's knowledge of the milder maladjustments and thus heighten his ability to deal with such problems. However, there is little discussion of the actual process of any psychotherapeutic approach, such as supportive or counseling methods. For example, there is a description of how a well-staffed child guidance clinic works with a school phobia problem, but little to guide the general practitioners (who may be some distance away from such a clinic), should he be presented with such a situation. Perhaps this shortcoming is to be expected when specialists—in this case, psychiatrists— attempt to reduce their techniques to purely descriptive, text-book-like material in an effort to impart their methods to physicians in other branches of medicine.

The North Shore Hospital has published several other lecture series which have been of value, and this volume may be of equal interest to many practitioners.

Virginia Huffer

RUSSELL, W. RITCHIE. *Brain Memory Learning.* Oxford University Press, Ox-

ford, England, 1959. 140 pp., illus. 18s (U. K.).

Through a series of essays consisting of "The Sensori-Motor System of the Brain," "The Word Mechanisms," "Consciousness: The Unconscious: Sleep," "Pain," and others, Professor Russell develops three major themes of brain function which give this work a true symphonic form. The pervading themes are: 1) that memory is the capacity for repetition, and that earliest memory is reinforced by subsequent memory processes; 2) that there is a bimodal excitation and inhibition physiology which extends from the simplest to the most complex units of the central nervous system function; 3) that the child's behavior patterns are effectively made in infancy and, therefore, amenable to direction and training.

The orchestration is achieved through Professor Russell's well-known work on traumatic lesions of the brain. He discusses the phenomena of traumatic amnesia and traumatic epilepsy in a less rigorous way than in his detailed publications, but this seems very proper as these data are ultilized primarily to develop his major themes. Although the "capacity to repeat" literally leads to logical difficulties in that any simple harmonic motion such as the rotation of the hands of a clock must come under the definition of "memory"; this first theme carries considerable conviction.

The neurophysiological theme, despite stating very recent work of Eccles, Magoun, and the centrencephalic concept of Penfield, really utilizes the basic and classical type of *hypothalamic-prefrontal system* conformation of the past, and consequently does not convey dynamic force to the presentation.

That a child can be superficially trained is incontestable, but whether it is most effective and rewarding to train children to be "good" and "normal" is certainly questionable; furthermore, whether training can greatly influence basic traits of any child is open to even more debate. Consequently, the third basic theme is one of hope, but with only a minimal amount of organized data to give strength and volume to the movement.

In appropriate places the text is illustrated by elegant Golgi and Golgi-Cox preparations. A fine photograph of a "traumatized" right cerebral hemisphere of the brain is garnered from the authoritative work of Dr. Ronald Norman.

As implied, this small book is not for the reader who is interested in, or expects to find, an encyclopedic discussion of brain anatomy and function, memory or learning processes. The importance of this work derives from two main sources: one, the scientific mediations of a representative and important contemporary neurologist; and two, the lucid, but largely negative demonstration that the most important, and consequently most beautiful, aspects of the relations of behavior and brain function are necessarily still, in 1959, inferential and speculative.

Robert Cohn

HILDEBRAND, J. H. *Science in the Making.* Columbia University Press, New York, 1957. 116 pp. $3.00

This series of four lectures by one of America's foremost chemists comprises one of the most delightful little books it has ever been this reviewer's privilege to read. The all-pervading curiosity, honesty, clarity and simple thoughtfulness of an outstanding mind are not often given the opportunity to present to a wide audience a plea for the preservation of intellectual values vital to the progress of our society. Part of the book is devoted to a fascinating description of Dr. Hildebrand's extensions of the theory of solubility. Most of it, however, necessitates no technical background on the part of the reader and considers problems being discussed widely at the present time.

Throughout the four lectures entitled "The Search for Knowledge," "False Paths,"

"Science has its Cathedrals" and "Knowledge and Power," there are statements that bear frequent repetition and careful thought. A few examples will serve to show the nature of the ideas dealt with.

"Most scientists would like to live in a society that had more respect..... for the power and beauty, not just the utility, of unrestricted human thought."

"Indeed, no two scientists work and think in just the same ways.... We proceed by common sense and ingenuity. There are no rules, only the principles of integrity and objectivity, with a complete rejection of all authority except that of fact."

"To be successful in unlocking the doors concealing nature's secrets, a person must have ingenuity. If he does not have the key for the lock he must not hesitate to try to pick it, to climb in a window or even to kick in a panel."

"One of the first principles of science is to be skeptical about sense impressions."

"Men are not all born equal, they do not have equal capacities for learning, nor for learning the same things."

With reference to the power of knowledge Professor Hildebrand states of an advanced student, that "the power he must develop is one to recognize and solve new problems, not to recite the known answers to old ones."

Many other statements here deserve being quoted. Dr. Hildebrand's suggestion that scientific thinking should become universal and should be the common-sense thinking of everyone applied to all phases of living, deserves widespread consideration. It strikes at the whole basic distortion in values of our "modern" society. He concludes with the following words the importance of which are only too obvious.

"An American citizen who is not alarmed by the contrast between the vitality of Soviet education in science and engineering, ... and the widespread flabbiness in American education, should not worry about atom bombs. The men in the Kremlin are hardly so stupid as to incur the risks of atomic warfare when all they need is the patience to await the fruits of an American school system degraded by teachers' colleges in which the doctrine taught, as a professor of education frankly informed his students, is different from the former idea of centering on the intellect, an idea which still holds in European countries. Unless the citizens of the United States regain a respect for intellectual achievement and provide intelligent teachers and administrators educated in the humanities and sciences for those schools in which they are now lacking, we are likely, I think, to see the power of knowledge gradually pass to hands that will wield it without the humane spirit that must be conjoined with knowledge if the knowledge is to be a blessing, not a curse."

What more can be said!

Robert G. Grenell

EYSENCK, H. J., GRANGER, G. W. AND BRENGELMANN, J. C. *Perceptual Processes and Mental Illness.* Maudsley Monographs, No. 2. Basic Books, Inc., New York, 1957. 144 pp., illus. $3.75

This is strictly an empirical and exploratory study in the crudest sense of these terms. This type of approach undoubtedly has a legitimate place in scientific investigation, but one may wonder if it is really what is needed in the field of perception and abnormal psychology at the present time. The expenditure of effort represented here was obviously enormous. That the results are at all commensurate, however, is a matter of serious doubt to this reviewer. The actual work of this monograph was completed several years ago under a U.S. Navy Bureau of Medicine and Surgery contract and is not formally related to Eysenck's more recent research at the Maudsley on introversion-extraversion.

The chief aim of the study was to determine whether visual and perceptual tests can discriminate between groups of normal individuals, neurotics, and psychotic pa-

tients, with a view to using such tests for "screening". and diagnostic purposes. The answer here provided to this question, which might seem a foregone conclusion to many, is that groups of normals, neurotics, and psychotics do, on the average, differ from one another on a number of perceptual tests.

The three groups that were compared were 106 normals (male soldiers), 20 neurotics, and 20 psychotics (patients diagnosed in the Maudsley Hospital). The groups differed slightly in age, but apparently not in intelligence. Each subject was given 13 paper-and-pencil tests (intelligence, personality questionnaires, etc.); some 43 visual-perceptual tests of which a number were relatively simple, *e.g.*, dark adaptation, visual acuity, fusion, convergence and accommodation, and others more complex, *e.g.*, various optical illusions, afterimages, etc.; and over a dozen autonomic and motor tests (sublingual temperature, salivary output, pulse rate, blood pressure, galvanic skin response, manual dexterity, statis ataxia, etc.). In all, about 123 measures on about 70 different tests were obtained for each subject. The differences between the means of the normals, neurotics, and psychotics on each of the 123 measures were tested for significance by analysis of variance. The results are briefly summarized in Table 1.

The statistical results are not as simple and clear-cut as they might appear. Variances are huge, and even where the group means differ, the overlap between groups is great. In most cases the variances of the three groups are markedly heterogeneous, which makes a strict interpretation of the analysis of variance impossible. Also, many of the measures are not independent, and so it is impossible to tell exactly to what extent the total number of significant discriminations attained by all the measures exceeded chance expectancy. No cross-validation was performed, making it uncertain which tests truly discriminate and which only appear to discriminate by virtue of sampling errors. Nevertheless, it seems clear from Table 1 that, overall, there are real differences between the groups in the realm of perceptual functioning.

TABLE 1

Proportion of Measures Discriminating Between Normals, Neurotics, and Psychotics in Analysis of Variance

Tests	No. of Measures	Significance Level of *F* Ratio			
		N.S.	0.05	0.01	0.001
Paper & Pencil	13	0.54	0.00	0.08	0.38
Simple Perceptual	45	0.40	0.20	0.20	0.20
Complex Perceptual	39	0.38	0.15	0.28	0.18
Autonomic	16	0.88	0.12	0.00	0.00
Motor	10	0.70	0.00	0.20	0.10
Total	123	0.49	0.14	0.19	0.18

Unfortunately this is as far as this study goes. Thus the major contribution of this monograph is that it has slightly increased our confidence in the widespread and long-held belief that normals, neurotics, and psychotic individuals differ in ways that are reflected at many different levels of functioning, including the visual-perceptual-motor levels. An interesting commentary on the unfruitfulness of the present study in taking us beyond this point is the fact that research has not been continued on these perceptual tests at the Maudsley and they are not used there diagnostically. Thus the high hopes expressed by Eysenck in the first chapter have not been fulfilled. (At present, simple paper-and-pencil tests are more effective for screening and diagnostic purposes than any combination of these perceptual tests.) In the final chapter Eysenck states: "More urgent, however, than improving along psychometric lines the practical diagnostic possibilities of these tests is the development of theoretical models of mental abnormality to explain the observed phenomena. Most existing theories may be adequate to deal with highly abstract concepts having little or no anchorage in behavior, but they do not enable us

to make predictions in the field covered in this monograph. This is an important point which we should like to emphasize. Scientific theories cannot choose the facts that they would wish to explain in any given field of study. If a theory fails to account for plainly relevant facts, this is a serious argument against it. The reader may like to try to explain the phenomena described here in terms of archetypes, oedipus complexes, life styles, or any other explanatory concepts used by 'dynamic' schools. If he finds, as we think he will, that fact and theory do not touch, then we may well doubt the value of theories that offer no guidance when they encounter experimentally ascertained facts regarding the perceptual behavior of normal, neurotic, and psychotic individuals." Yet Eysenck himself offers not even a hint along theoretical lines that might help to make sense out of these masses of data he has collected.

What is needed now is a truly experimental, functionalistic analysis of the few most promising of these perceptual tests, so as to determine as many of the sources of variance as possible. It is likely that much, perhaps most, of the variance in the present study is "error" variance. (The reliability of the measures is not known.) Investigations in this area will probably have to remain in the realm of "pure research" for quite some time.

A factor analysis was carried out on 77 of these measures in the normal group. Because of the apparently low reliability of many of the measures, the non-linearity of the correlations between measures, and the small number of subjects in relation to the number of variables, this factor analysis was conspicuously unfruitful. It is most difficult, probably impossible, to interpret any of the five factors that were extracted.

The monograph incidentally contains some features of value and interest that can be especially recommended to American workers in this field. Brengelmann introduces a number of tests of complex perceptual functioning from Germany that are little known in this country. Many of these tests have already been used in personality studies, and Brengelmann attempts to relate to the present study the hypotheses and findings regarding perception and personality based largely on German research. This section is the most psychological and perhaps the most valuable part of the monograph. Also, the description (in Chapter IV) of the Nufferno Test, which measures intelligence in terms of level, speed, and persistence, is worth noting by American investigators. This test, devised at the Maudsley by Furneaux, is a sound and important innovation in intelligence testing which merits greater recognition and use in the United States.

Arthur R. Jensen